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(54) Title: INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

## (57) Abstract

The present invention is directed to compounds which inhibit farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. The invention is further directed to chemotherapeutic compositions containing the compounds of this invention and methods for inhibiting farnesyl-protein transferase and the farnesylation of the oncogene protein Ras.

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TITLE OF THE INVENTION

INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

BACKGROUND OF THE INVENTION

5        The Ras proteins (Ha-Ras, Ki4a-Ras, Ki4b-Ras and N-Ras) are part of a signalling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP.

10      Upon growth factor receptor activation Ras is induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and

15      D.M. Willumsen, *Ann. Rev. Biochem.* 62:851-891 (1993)). Mutated *ras* genes (Ha-*ras*, Ki4a-*ras*, Ki4b-*ras* and N-*ras*) are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit

20      a growth stimulatory signal.

         Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus

25      contains a sequence motif termed a "CAAX" or "Cys-Aaa<sup>1</sup>-Aaa<sup>2</sup>-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al.*, *Nature* 310:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein transferase, which catalyze the alkylation of the cysteine residue of the CAAX motif with a C<sub>15</sub> or C<sub>20</sub> isoprenoid, respectively. (S. Clarke., *Ann. Rev. Biochem.* 61:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics* 30:209-237 (1992)). The Ras protein is one of several proteins that are known to undergo post-translational farnesyl-

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ation. Other farnesylated proteins include the Ras-related GTP-binding proteins such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem.* 269, 14182 (1994) have identified a peroxisome associated protein Pxf which is also 5 farnesylated. James, et al., have also suggested that there are farnesylated proteins of unknown structure and function in addition to those listed above.

Inhibition of farnesyl-protein transferase has been shown to block the growth of Ras-transformed cells in soft agar and 10 to modify other aspects of their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the Ras oncoprotein intracellularly (N.E. Kohl et al., *Science*, 260:1934-1937 (1993) and G.L. James et al., *Science*, 260:1937-1942 (1993). Recently, it has been shown that an 15 inhibitor of farnesyl-protein transferase blocks the growth of *ras*-dependent tumors in nude mice (N.E. Kohl et al., *Proc. Natl. Acad. Sci. U.S.A.*, 91:9141-9145 (1994) and induces regression of mammary and salivary carcinomas in *ras* transgenic mice (N.E. Kohl et al., *Nature Medicine*, 1:792-797 (1995).

20 Indirect inhibition of farnesyl-protein transferase *in vivo* has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock et al., *ibid*; Casey et al., *ibid*; Schafer et al., *Science* 245:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including 25 farnesyl pyrophosphate. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss et al., *Cell*, 62:81-88 (1990); Schaber et al., *J. Biol. Chem.*, 265:14701-14704 (1990); Schafer et al., *Science*, 249:1133-1139 (1990); Manne et al., *Proc. Natl. Acad. Sci. USA*, 87:7541-7545 (1990)). Inhibition of farnesyl pyrophosphate biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in cultured cells. However, direct inhibition of farnesyl-protein transferase would be more specific and attended by fewer side 30 effects than would occur with the required dose of a general inhibitor

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of isoprene biosynthesis.

Inhibitors of farnesyl-protein transferase (FPTase) have been described in four general classes (S. Graham, *Expert Opinion Ther. Patents*, (1995) 5:1269-1285). The first are analogs of farnesyl diphosphate (FPP), while a second class of inhibitors is related to the protein substrates (e.g., Ras) for the enzyme. Bisubstrate inhibitors and inhibitors of farnesyl-protein transferase that are non-competitive with the substrates have also been described. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber *et al.*, *ibid*; Reiss *et. al.*, *ibid*; Reiss *et al.*, *PNAS*, 88:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al.*, *Science*, 260:1934-1937 (1993); Graham, *et al.*, *J. Med. Chem.*, 37, 725 (1994)). In general, deletion of the thiol from a CAAX derivative has been shown to dramatically reduce the inhibitory potency of the compound. However, the thiol group potentially places limitations on the therapeutic application of FPTase inhibitors with respect to pharmacokinetics, pharmacodynamics and toxicity. Therefore, a functional replacement for the thiol is desirable.

It has recently been disclosed that certain tricyclic compounds which optionally incorporate a piperidine moiety are inhibitors of FPTase (WO 95/10514, WO 95/10515 and WO 95/10516). Imidazole-containing inhibitors of farnesyl protein transferase have also been disclosed (WO 95/09001 and EP 0 675 112 A1).

It has recently been reported that farnesyl-protein transferase inhibitors are inhibitors of proliferation of vascular smooth muscle cells and are therefore useful in the prevention and therapy of arteriosclerosis and diabetic disturbance of blood vessels (JP H7-112930).

It is, therefore, an object of this invention to develop

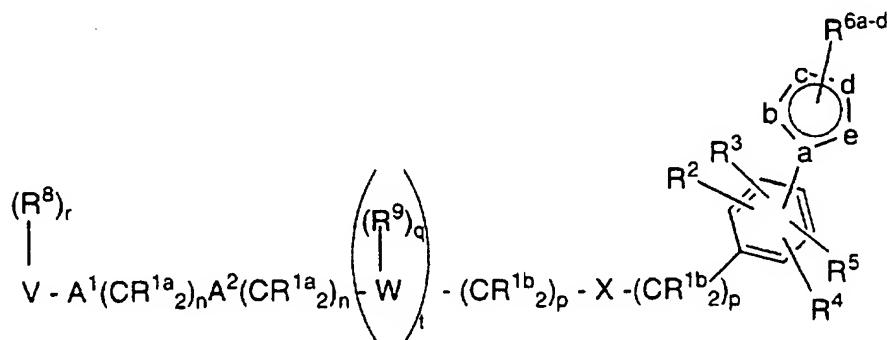
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low molecular weight compounds that will inhibit farnesyl-protein transferase and thus, the post-translational farnesylation of proteins. It is a further object of this invention to develop chemotherapeutic compositions containing the compounds of this invention and methods 5 for producing the compounds of this invention.

### SUMMARY OF THE INVENTION

The present invention comprises peptidomimetic arylheteroaryl-containing compounds which inhibit the farnesyl-protein 10 transferase. Further contained in this invention are chemotherapeutic compositions containing these farnesyl transferase inhibitors and methods for their production.

The compounds of this invention are illustrated by the 15 formula A:

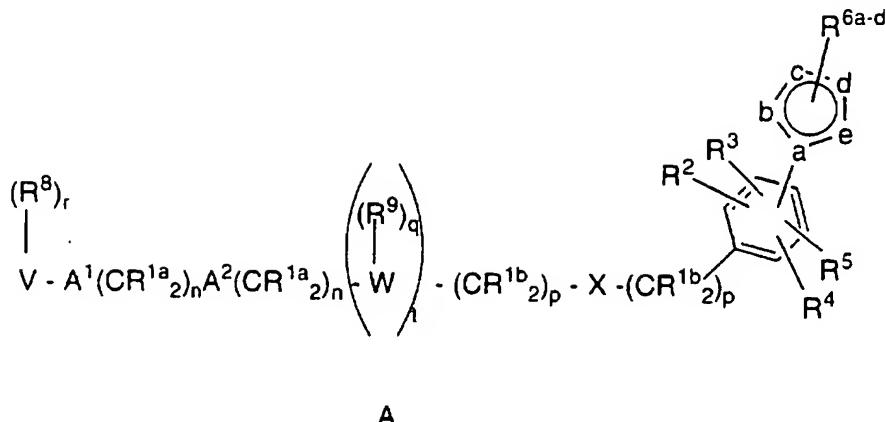


A

### DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition 20 of farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. In a first embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula A:

- 5 -



wherein:

a is N or C;

5

from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH, O or S;

10 R<sup>1a</sup> and R<sup>1b</sup> are independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, R<sup>11</sup>C(O)O-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN,

15

NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,

- c) unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are independently selected from:

20

- a) hydrogen,

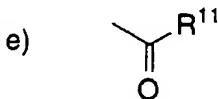
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- 7 -

$R^{12}O$ -,  $R^{11}S(O)m$ -,  $R^{10}C(O)NR^{10}$ -,  $(R^{10})_2NC(O)$ -,  
 $R^{10}N-C(NR^{10})$ -, CN,  $R^{10}C(O)$ -, N<sub>3</sub>, -N( $R^{10}$ )<sub>2</sub>, and  
 $R^{11}OC(O)-NR^{10}$ ;

5  $R^7$  is selected from: H; C<sub>1</sub>-4 alkyl, C<sub>3</sub>-6 cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

- 10 a) C<sub>1</sub>-4 alkoxy,
- b) aryl or heterocycle,
- c) halogen,
- d) HO,



- f)  $-SO_2R^{11}$
- g)  $N(R^{10})_2$  or
- h) C<sub>1</sub>-4 perfluoroalkyl;

15  $R^8$  is independently selected from:

- a) hydrogen,
- b) aryl, substituted aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, perfluoroalkyl, F, Cl, Br, 20 R<sub>10</sub>O<sub>-, R<sup>11</sup>S(O)m<sub>-</sub>, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and</sub>
- c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, perfluoroalkyl, F, Cl, Br, R<sub>10</sub>O<sub>-, R<sup>11</sup>S(O)m<sub>-</sub>, R<sup>10</sup>C(O)NH<sub>-</sub>, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>10</sup>OC(O)NH<sub>-</sub>;</sub>

25 provided that when  $R^8$  is heterocycle, attachment of  $R^8$  to V is 30 through a substitutable ring carbon;

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R9 is independently selected from:

- a) hydrogen,
- b) C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, halogen, R<sup>11</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and
- c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,

10

R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

15 R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

20

A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>C(O)-, O, -N(R<sup>10</sup>)-, -S(O)<sub>2</sub>N(R<sup>10</sup>)-, -N(R<sup>10</sup>)S(O)<sub>2</sub>- or S(O)<sub>m</sub>;

25

V is selected from:

- a) hydrogen,
- b) heterocycle,
- c) aryl,
- d) C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C<sub>2</sub>-C<sub>20</sub> alkenyl,

30

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provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;

provided that when V is heterocycle, attachment of V to R<sup>8</sup> and to A<sup>1</sup> is through a substitutable ring carbon;

5

W is a heterocycle;

X is a bond, -CH=CH-, O, -C(=O)-, -C(O)NR<sup>7</sup>-, -NR<sup>7</sup>C(O)-, -C(O)O-,  
10 -OC(O)-, -C(O)NR<sup>7</sup>C(O)-, -NR<sup>7</sup>-, -S(O)<sub>2</sub>N(R<sup>10</sup>)-,  
-N(R<sup>10</sup>)S(O)<sub>2</sub>- or -S(=O)<sub>m</sub>-;

m is 0, 1 or 2;

n is independently 0, 1, 2, 3 or 4;

p is independently 0, 1, 2, 3 or 4;

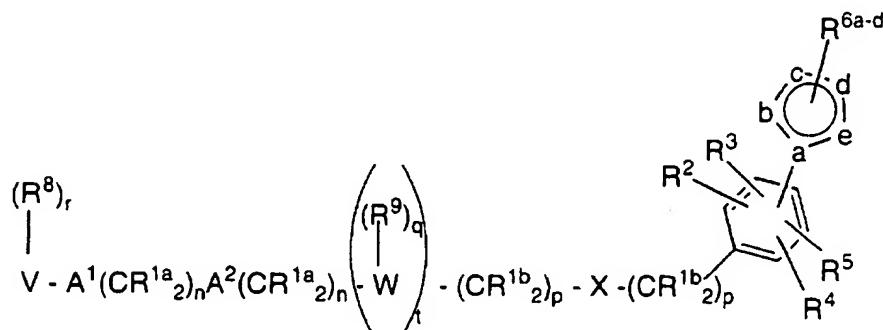
15 q is 0, 1, 2 or 3;

r is 0 to 5, provided that r is 0 when V is hydrogen; and

t is 0 or 1;

or the pharmaceutically acceptable salts thereof.

20 A preferred embodiment of the compounds of this invention is illustrated by the following formula:



A

wherein:

- 10 -

a is N or C;

from 0-4 of b, c, d and e are independently N, NH, O and S, and the  
5 remaining b, c, d and e atoms are independently CH, provided that if a  
is C, then at least one of b, c, d or e is independently N, NH, O or S;

R<sup>1a</sup> is independently selected from: hydrogen, C<sub>3</sub>-C<sub>10</sub> cycloalkyl,  
R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>1</sub>-C<sub>6</sub> alkyl;

10 R<sup>1b</sup> is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>,  
F or C<sub>2</sub>-C<sub>6</sub> alkenyl,
- c) unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the  
15 substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from  
unsubstituted or substituted aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub>  
cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O- and -N(R<sup>10</sup>)<sub>2</sub>;

R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are independently selected from:

- 20 a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or  
substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub>  
alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl,  
R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-,  
25 R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>,  
or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl;
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the  
30 substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or  
substituted aryl, unsubstituted or substituted heterocyclic,  
C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,  
R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-,  
R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and  
R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

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provided that when R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> or R<sup>5</sup> is unsubstituted or substituted heterocycle, attachment of R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> or R<sup>5</sup> to the phenyl ring is through a substitutable heterocycle ring carbon;

5

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

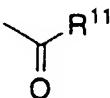
- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl;
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

10

R<sup>7</sup> is selected from: H; C<sub>1</sub>-4 alkyl, C<sub>3</sub>-6 cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

15

- a) C<sub>1</sub>-4 alkoxy,
- b) aryl or heterocycle,
- c) halogen,
- d) HO,
- e)



20

- f) -SO<sub>2</sub>R<sup>11</sup>
- g) N(R<sup>10</sup>)<sub>2</sub> or

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h) C<sub>1</sub>-4 perfluoroalkyl;

R<sub>8</sub> is independently selected from:

- a) hydrogen,
- 5 b) aryl, substituted aryl, heterocycle, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and
- 10 c) C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,  
provided that when R<sub>8</sub> is heterocycle, attachment of R<sub>8</sub> to V is through a substitutable ring carbon;

15 R<sub>9</sub> is independently selected from:

- a) hydrogen,
- b) C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, R<sup>11</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and
- 20 c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, CN, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,

25

R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

30

R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl,

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2-aminoethyl and 2,2,2-trifluoroethyl;

A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR<sup>10</sup>-, O, -N(R<sup>10</sup>)-, or S(O)<sub>m</sub>;

5

V is selected from:

- a) hydrogen,
- b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,
- c) aryl,
- d) C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C<sub>2</sub>-C<sub>20</sub> alkenyl, and

10 15 provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;  
provided that when V is heterocycle, attachment of V to R<sup>8</sup> and to A<sup>1</sup> is through a substitutable ring carbon;

20 25 W is a heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, triazolyl or isoquinolinyl;

X is a bond, O, -C(=O)-, -CH=CH-, -C(O)NR<sup>7</sup>-, -NR<sup>7</sup>C(O)-, -NR<sup>7</sup>-, -S(O)<sub>2</sub>N(R<sup>10</sup>)-, -N(R<sup>10</sup>)S(O)<sub>2</sub>- or -S(=O)<sub>m</sub>-;

30 m is 0, 1 or 2;

n is independently 0, 1, 2, 3 or 4;

q is independently 0, 1, 2 or 3;

p is 0, 1, 2, 3 or 4;

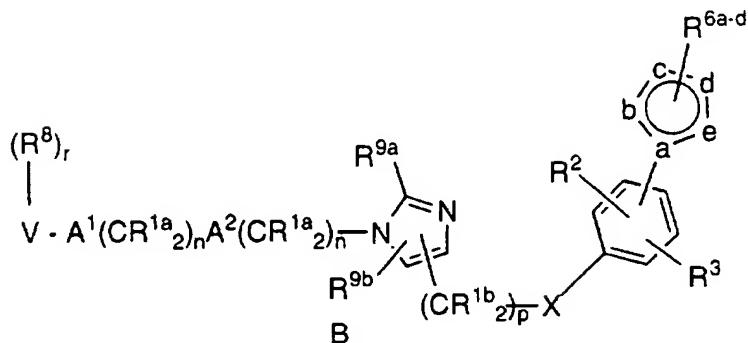
r is 0 to 5, provided that r is 0 when V is hydrogen; and

t is 0 or 1;

or the pharmaceutically acceptable salts thereof.

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A preferred embodiment of the compounds of this invention are illustrated by the formula B:



wherein:

5

a is N or C;

from 0-4 of b, c, d and e are independently N, NH, O and S, and the  
10 remaining b, c, d and e atoms are independently CH, provided that if a  
is C, then at least one of b, c, d or e is independently N, NH, O or S;

R1a is independently selected from: hydrogen, C3-C10 cycloalkyl,  
R10O-, -N(R10)2, F or C1-C6 alkyl;

15 R1b is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C3-C10 cycloalkyl, R10O-, -N(R10)2,  
F or C2-C6 alkenyl,

c) unsubstituted or substituted C1-C6 alkyl wherein the  
20 substituent on the substituted C1-C6 alkyl is selected from  
unsubstituted or substituted aryl, heterocycle, C3-C10  
cycloalkyl, C2-C6 alkenyl, R10O- and -N(R10)2;

R2 and R3 are independently selected from:

25 a) hydrogen,

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5 b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup>2N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,  
c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup>2N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-,  
10 provided that when R<sup>2</sup> or R<sup>3</sup> is unsubstituted or substituted heterocycle, attachment of R<sup>2</sup> or R<sup>3</sup> to the phenyl ring is through a substitutable heterocycle ring carbon;  
15

R6a, R6b, R6c and R6d are independently selected from:

20           a) hydrogen,  
              b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup>2N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,  
              c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
              d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup>2N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

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R<sup>8</sup> is independently selected from:

- a) hydrogen,
- b) 5 aryl, substituted aryl, heterocycle, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and
- c) 10 C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,

provided that when R<sup>8</sup> is heterocycle, attachment of R<sup>8</sup> to V is through a substitutable ring carbon;

R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, trifluoromethyl 15 and halogen;

R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

20 R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, 25 C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>C(O)-, O, -N(R<sup>10</sup>)-, or 30 S(O)<sub>m</sub>;

V is selected from:

- a) hydrogen,

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- b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,
- c) aryl,
- 5 d) C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C<sub>2</sub>-C<sub>20</sub> alkenyl, and

provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;

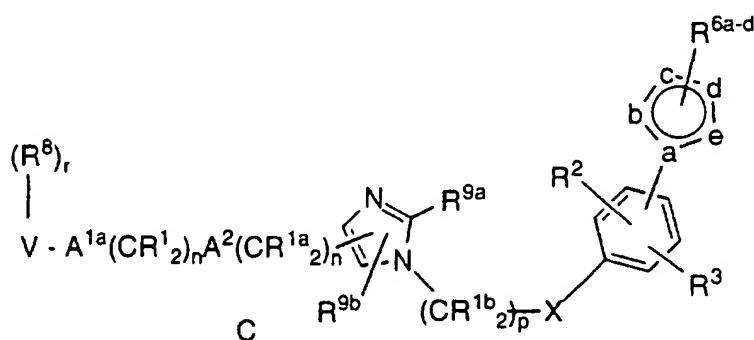
10 provided that when V is heterocycle, attachment of V to R<sup>8</sup> and to A<sup>1</sup> is through a substitutable ring carbon;

X is a bond, -CH=CH-, -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>C(O)-, -NR<sup>10</sup>-, O or -C(=O)-;

15 m is 0, 1 or 2;  
 n is independently 0, 1, 2, 3 or 4;  
 p is 0, 1, 2, 3 or 4; and  
 r is 0 to 5, provided that r is 0 when V is hydrogen;

20 or the pharmaceutically acceptable salts thereof.

Another preferred embodiment of the compounds of this invention are illustrated by the formula C:



25 wherein:

a is N or C;

from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH, O or S;

5

R<sup>1a</sup> is independently selected from: hydrogen, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>1b</sup> is independently selected from:

- 10 a) hydrogen,
- b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>2</sub>-C<sub>6</sub> alkenyl,
- c) unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O- and -N(R<sup>10</sup>)<sub>2</sub>;

15

R<sup>2</sup> and R<sup>3</sup> are independently selected from:

- 20 a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN(R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- 25 c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

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provided that when R<sup>2</sup> or R<sup>3</sup> is unsubstituted or substituted heterocycle, attachment of R<sup>2</sup> or R<sup>3</sup> to the phenyl ring is through a substitutable heterocycle ring carbon;

5 R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN(R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

R<sup>8</sup> is independently selected from:

- a) hydrogen,
- b) aryl, substituted aryl, heterocycle, substituted heterocycle C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and
- c) C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-;

provided that when R<sup>8</sup> is heterocycle, attachment of R<sup>8</sup> to V is through a substitutable ring carbon;

- 20 -

R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, trifluoromethyl and halogen;

5 R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

10 R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

15 A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(Ö)NR<sup>10</sup>-, O, -N(R<sup>10</sup>)-, or S(O)<sub>m</sub>;

V is selected from:

20 a) hydrogen,  
b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl triazolyl and thienyl,  
c) aryl,  
d) C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are  
25 replaced with a heteroatom selected from O, S, and N, and  
e) C<sub>2</sub>-C<sub>20</sub> alkenyl, and

provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;

30 provided that when V is heterocycle, attachment of V to R<sup>8</sup> and to A<sup>1</sup> is through a substitutable ring carbon;

X is a bond, -CH=CH-, -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>C(O)-, -NR<sup>10</sup>-, O or -C(=O)-;

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m is 0, 1 or 2;

n is independently 0, 1, 2, 3 or 4;

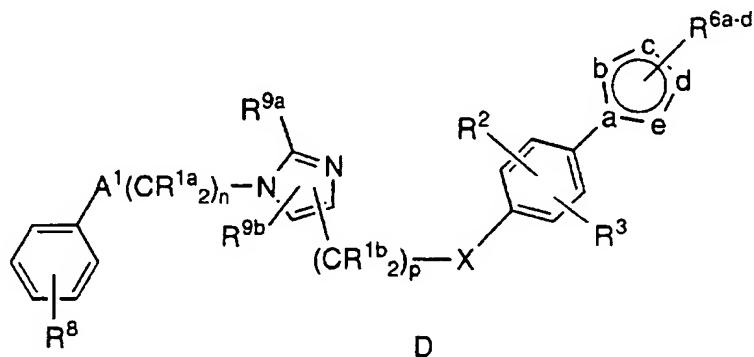
p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond, -NR<sup>10</sup>-, -NR<sup>10</sup>- or O; and

5 r is 0 to 5, provided that r is 0 when V is hydrogen;

or the pharmaceutically acceptable salts thereof.

In a more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula

10 D:



wherein:

a is N or C;

15

from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH, O or S;

20 R<sup>1a</sup> is independently selected from: hydrogen, C<sub>3</sub>-C<sub>10</sub> cycloalkyl or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>1b</sup> is independently selected from:

a) hydrogen,

25 b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>2</sub>-C<sub>6</sub> alkenyl,

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c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O-, or -N(R<sup>10</sup>)<sub>2</sub>;

5 R<sup>2</sup> is selected from:

a) hydrogen,  
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl,  
10 R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,  
c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the  
15 substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and  
20 R<sup>11</sup>OC(O)-NR<sup>10</sup>-,

provided that when R<sup>2</sup> is unsubstituted or substituted heterocycle, attachment of R<sup>2</sup> to the phenyl ring is through a substitutable heterocycle ring carbon;

25 R<sup>3</sup> is selected from H, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl and CF<sub>3</sub>;

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

a) hydrogen,  
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl,  
30 R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,

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- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

10 R<sup>8</sup> is independently selected from:

- a) hydrogen,
- b) aryl, substituted aryl, heterocycle, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and
- c) C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-;

15 provided that when R<sup>8</sup> is heterocycle, attachment of R<sup>8</sup> to V is  
20 through a substitutable ring carbon;

R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, halogen, CF<sub>3</sub> or methyl;

25 R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

30 R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

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$A^1$  is selected from: a bond,  $-C(O)-$ ,  $O$ ,  $-N(R^{10})-$  or  $S(O)m$ ;

$X$  is a bond,  $-CH=CH-$ ,  $-C(O)NR^{10}-$ ,  $-NR^{10}C(O)-$ ,  $-N(R^{10})-$ ,  $O$  or  $-C(=O)-$ ;

5

$n$  is 0 or 1; provided that  $n$  is not 0 if  $A^1$  is a bond,  $O$ ,  $-N(R^{10})-$ , or  $S(O)m$ ;

$m$  is 0, 1 or 2; and

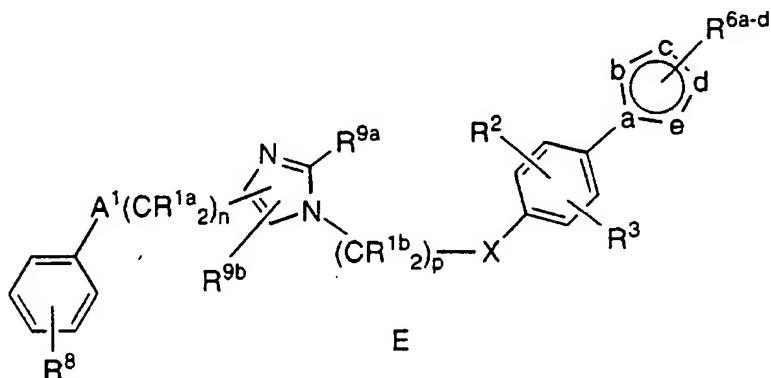
$p$  is 0, 1, 2, 3 or 4;

10

or the pharmaceutically acceptable salts thereof.

In another more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula E:

15



wherein:

$a$  is  $N$  or  $C$ ;

20 from 0-4 of  $b$ ,  $c$ ,  $d$  and  $e$  are independently  $N$ ,  $NH$ ,  $O$  and  $S$ , and the remaining  $b$ ,  $c$ ,  $d$  and  $e$  atoms are independently  $CH$ , provided that if  $a$  is  $C$ , then at least one of  $b$ ,  $c$ ,  $d$  or  $e$  is independently  $N$ ,  $NH$ ,  $O$  or  $S$ ;

$R^{1a}$  is independently selected from: hydrogen,  $R^{10}O-$ ,  $-N(R^{10})_2$ ,  $F$ ,

25  $C_3-C_{10}$  cycloalkyl or  $C_1-C_6$  alkyl;

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R<sup>1b</sup> is independently selected from:

- a) hydrogen,
- b) 5 aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>2</sub>-C<sub>6</sub> alkenyl,
- c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O-, or -N(R<sup>10</sup>)<sub>2</sub>;

10 R<sup>2</sup> is selected from:

- a) hydrogen,
- b) 15 unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- c) 20 unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) 25 substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

provided that when R<sup>2</sup> is unsubstituted or substituted heterocycle, attachment of R<sup>2</sup> to the phenyl ring is through a substitutable heterocycle ring carbon;

30 R<sup>3</sup> is selected from H, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl and CF<sub>3</sub>;

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

- a) hydrogen,

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5 b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup>2N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,

c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,

d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup>2N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

15 R8 is independently selected from:

20 a) hydrogen,  
b) aryl, substituted aryl, heterocycle, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, R<sup>10</sup>O<sup>-</sup>, R<sup>10</sup>C(O)NR<sup>10</sup><sup>-</sup>, CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)<sup>-</sup>, R<sup>10</sup>C(O)<sup>-</sup>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup><sup>-</sup>, and  
c) C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>10</sup>O<sup>-</sup>, R<sup>10</sup>C(O)NR<sup>10</sup><sup>-</sup>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)<sup>-</sup>, R<sup>10</sup>C(O)<sup>-</sup>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup><sup>-</sup>;

25 . provided that when R8 is heterocycle, attachment of R8 to V is through a substitutable ring carbon;

R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, halogen, CF<sub>3</sub> or methyl;

30 R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

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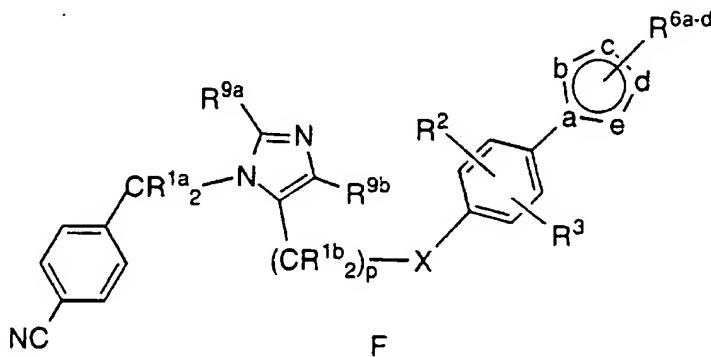
5             $R^{12}$  is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

X is a bond, -CH=CH-, -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>C(O)-, -N(R<sup>10</sup>)-, O or -C(=O)-;

10    n is            0 or 1;  
       m is            0, 1 or 2; and  
       p is            0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond or O;

15            or the pharmaceutically acceptable salts thereof.

15            In a further embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula F:



wherein:

20    a is N or C;

from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH, O or S;

25

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R<sup>1a</sup> is independently selected from: hydrogen, C<sub>3</sub>-C<sub>10</sub> cycloalkyl or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>1b</sup> is independently selected from:

5        a)    hydrogen,  
          b)    aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub> or F,  
          c)    C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, or -N(R<sup>10</sup>)<sub>2</sub>;

10

R<sup>2</sup> is selected from:

15        a)    hydrogen,  
          b)    unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,  
          c)    unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
20        d)    substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and  
25        R<sup>11</sup>OC(O)-NR<sup>10</sup>-,  
provided that when R<sup>2</sup> is unsubstituted or substituted heterocycle, attachment of R<sup>2</sup> to the phenyl ring is through a substitutable heterocycle ring carbon;

30

R<sup>3</sup> is selected from H, halogen, CH<sub>3</sub> and CF<sub>3</sub>;

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

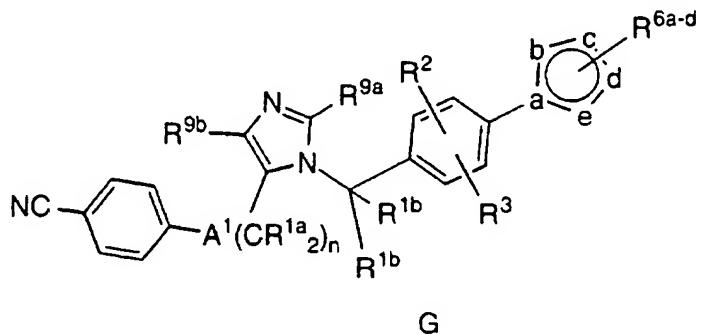
a)    hydrogen.

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or the pharmaceutically acceptable salts thereof.

In a further embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula G:



5 wherein:

a is N or C;

10 from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH, O or S;

15 R<sup>1a</sup> is independently selected from: hydrogen, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F, C<sub>3</sub>-C<sub>10</sub> cycloalkyl or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>1b</sup> is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle or C<sub>3</sub>-C<sub>10</sub> cycloalkyl,
- c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl,

20 heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O-, or -N(R<sup>10</sup>)<sub>2</sub>;

R<sup>2</sup> is selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub>

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alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-;

5       c)    unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
d)    substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the  
substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or  
substituted aryl, unsubstituted or substituted heterocyclic,  
C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,  
10      R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-,  
R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and  
R<sup>11</sup>OC(O)-NR<sup>10</sup>-;  
provided that when R<sup>2</sup> is unsubstituted or substituted heterocycle,  
attachment of R<sup>2</sup> to the phenyl ring is through a  
15      substitutable heterocycle ring carbon;

R<sup>3</sup> is selected from H, halogen, CH<sub>3</sub> and CF<sub>3</sub>;

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

20      a)    hydrogen,  
b)    unsubstituted or substituted aryl, unsubstituted or  
substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub>  
alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl,  
R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-,  
25      R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>,  
or R<sup>11</sup>OC(O)NR<sup>10</sup>-,  
c)    unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
d)    substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the  
substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or  
30      substituted aryl, unsubstituted or substituted heterocyclic,  
C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,  
R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-,  
R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and  
R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

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R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, halogen, CF<sub>3</sub> or methyl;

5 R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

10 R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

15 A<sup>1</sup> is selected from: a bond, -C(O)-, O, -N(R<sup>10</sup>)-, or S(O)<sub>m</sub>;

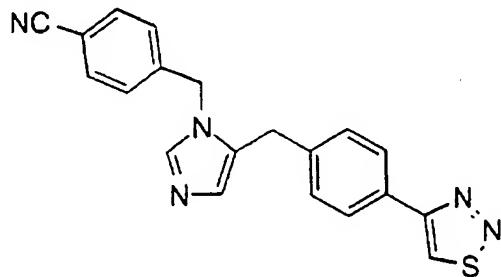
m is 0, 1 or 2; and

n is 0 or 1;

20 or the pharmaceutically acceptable salts thereof.

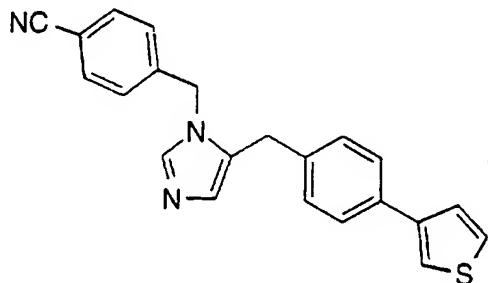
Specific examples of the compounds of the invention are:

25 1-(4-(1,2,3-Thiadiazolyl)-phenylmethyl)-5-(4-cyanobenzyl) imidazole



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1-(4-[Thien-3-yl]phenylmethyl)-5-(4-cyanobenzyl)imidazole



5 or the pharmaceutically acceptable salts thereof.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. When any variable 10 (e.g. aryl, heterocycle, R<sup>1a</sup>, R<sup>1b</sup> etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" and the alkyl portion of aralkyl and 15 similar terms, is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge.

As used herein, "cycloalkyl" is intended to include non-aromatic cyclic hydrocarbon groups having the specified number of 20 carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

"Alkenyl" groups include those groups having the specified 25 number of carbon atoms and having one or several double bonds. Examples of alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, isoprenyl, farnesyl, geranyl, geranylgeranyl and the like.

"Alkynyl" groups include those groups having the specified number of carbon atoms and having one triple bonds. Examples of alkynyl groups include acetylene, 2-butynyl, 2-pentynyl, 3-pentynyl and the like.

5 "Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo.

As used herein, "aryl," and the aryl portion of aralkyl and aroyl, is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic.

10 Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl.

The term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 15 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring 20 may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, 25 dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopyrrolidinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl.

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As used herein, "heteroaryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group consisting of N, O, and S. Examples of such heterocyclic elements include, but are not limited to, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, thienothienyl, and thienyl.

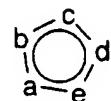
As used herein in the definition of R<sup>7</sup>, the substituted C<sub>1-8</sub> alkyl, substituted C<sub>3-6</sub> cycloalkyl, substituted aroyl, substituted aryl, substituted heteroaroyl, substituted arylsulfonyl, substituted heteroarylsulfonyl and substituted heterocycle include moieties containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound.

As used herein, when no specific substituents are set forth, the terms "substituted aryl", "substituted heterocycle" and "substituted cycloalkyl" are intended to include the cyclic group which is substituted on a substitutable ring carbon atom with 1 or 2 substituents selected from the group which includes but is not limited to F, Cl, Br, CF<sub>3</sub>, NH<sub>2</sub>, N(C<sub>1-C6</sub> alkyl)<sub>2</sub>, NO<sub>2</sub>, CN, (C<sub>1-C6</sub> alkyl)O-, -OH, (C<sub>1-C6</sub> alkyl)S(O)<sub>m</sub>-, (C<sub>1-C6</sub> alkyl)C(O)NH-, H<sub>2</sub>N-C(NH)-, (C<sub>1-C6</sub> alkyl)C(O)-, (C<sub>1-C6</sub> alkyl)OC(O)-, N<sub>3</sub>-(C<sub>1-C6</sub> alkyl)OC(O)NH-, phenyl, pyridyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furyl, isothiazolyl and C<sub>1-C20</sub> alkyl.

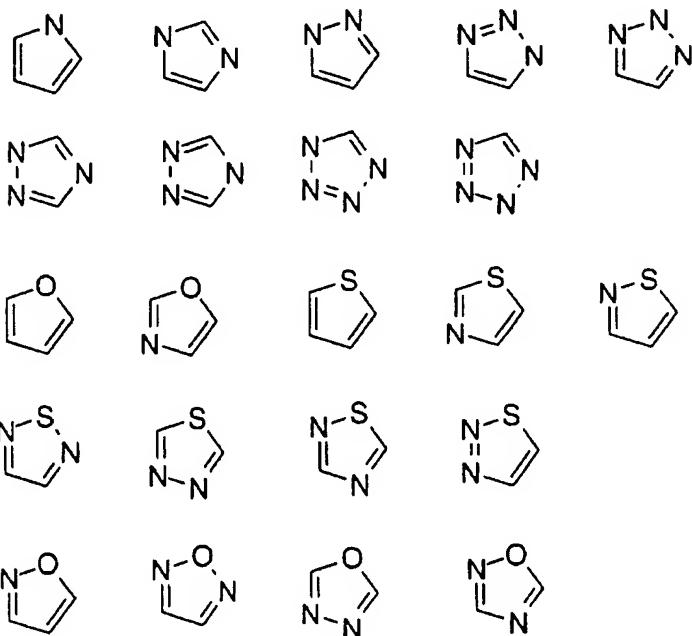
Lines drawn into the ring systems from substituents (such as from R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> etc.) indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

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The moiety designated by the following structure

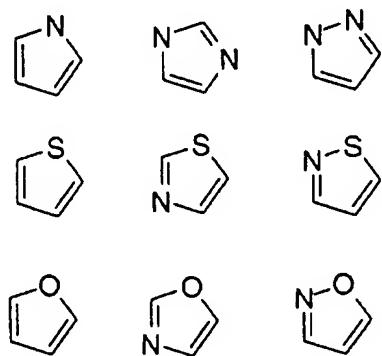


represents an aromatic 5-membered heterocyclic ring and includes the following ring systems:



5

Preferably the aromatic 5-membered heterocyclic ring is selected from:



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Preferably,  $R^{1a}$  and  $R^{1b}$  are independently selected from: hydrogen,  $R^{11}C(O)O-$ ,  $-N(R^{10})_2$ ,  $R^{10}C(O)NR^{10}-$ ,  $R^{10}O-$  or unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted phenyl,  $-N(R^{10})_2$ ,  $R^{10}O-$  and  $R^{10}C(O)NR^{10}-$ .

5 Preferably,  $R^2$  is selected from:

- a) hydrogen,
- b) C<sub>3</sub>-C<sub>10</sub> cycloalkyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl,  $R^{12}O-$ , CN, NO<sub>2</sub>,  $R^{10}C(O)-$  or  $-N(R^{10})_2$ ,
- 10 c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,  $R^{12}O-$ ,  $R^{11}S(O)m-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,  $R^{10}N-C(NR^{10})-$ , CN,  $R^{10}C(O)-$ , N<sub>3</sub>,  $-N(R^{10})_2$ , and  $R^{11}OC(O)-NR^{10}-$ .

15 Preferably,  $R^3$  is selected from: hydrogen, halogen, trifluoromethyl, trifluoromethoxy and C<sub>1</sub>-C<sub>6</sub> alkyl.

20 Preferably,  $R^4$  and  $R^5$  are hydrogen.

25 Preferably,  $R^{6a}$ ,  $R^{6b}$ ,  $R^{6c}$  and  $R^{6d}$  are independently selected from:

- a) hydrogen,
- b) C<sub>3</sub>-C<sub>10</sub> cycloalkyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl,  $R^{12}O-$ ,  $R^{11}S(O)m-$ , CN, NO<sub>2</sub>,  $R^{10}C(O)-$  or  $-N(R^{10})_2$ ,
- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl;
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl,  $R^{12}O-$ ,  $R^{11}S(O)m-$ ,  $R^{10}C(O)-$  or  $-N(R^{10})_2$ .

30 Preferably,  $R^8$  is independently selected from:

- a) hydrogen, and
- b) aryl, substituted aryl, heterocycle, substituted heterocycle, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl or CN.

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Preferably,  $R^9$  is hydrogen, halogen,  $CF_3$  or methyl.

Preferably,  $R^{10}$  is selected from H, C1-C6 alkyl and

benzyl.

Preferably,  $A^1$  and  $A^2$  are independently selected from:

5 a bond,  $-\text{C}(\text{O})\text{NR}^{10}-$ ,  $-\text{NR}^{10}\text{C}(\text{O})-$ , O,  $-\text{N}(\text{R}^{10})-$ ,  $-\text{S}(\text{O})_2\text{N}(\text{R}^{10})-$  and  $-\text{N}(\text{R}^{10})\text{S}(\text{O})_2-$ .

Preferably, V is selected from hydrogen, heterocycle and aryl. More preferably, V is phenyl.

Preferably, W is selected from imidazolinyl, imidazolyl,

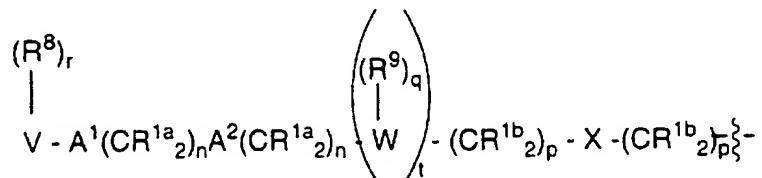
10 oxazolyl, pyrazolyl, ppyrrolidinyl, thiazolyl and pyridyl. More preferably, W is selected from imidazolyl and pyridyl.

Preferably,  $n$  and  $r$  are independently 0, 1, or 2.

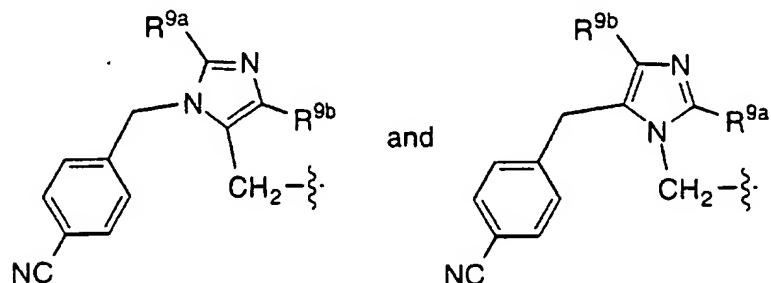
Preferably  $s$  is 0.

Preferably  $t$  is 1.

## 15 Preferably, the moiety



is selected from:



It is intended that the definition of any substituent or variable (e.g., R<sub>1</sub>a, R<sub>1</sub>b, R<sup>9</sup>, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, -N(R<sub>10</sub>)<sub>2</sub> represents -NHH, -NHCH<sub>3</sub>, -NHC<sub>2</sub>H<sub>5</sub>, etc. It is understood that substituents and substitution patterns on the compounds

of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

5        The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, 10 sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, 15 isethionic, trifluoroacetic and the like.

      The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared either by ion exchange 20 chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

      Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the Schemes 1-22, 25 in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R<sup>2</sup>, R<sup>6</sup> and R<sup>8</sup>, as shown in the Schemes, represent the substituents R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup>, R<sup>6d</sup> and R<sup>8</sup>; although only one such R<sup>2</sup>, R<sup>6</sup> 30 or R<sup>8</sup> is present in the intermediates and products of the schemes, it is understood that the reactions shown are also applicable when such aryl or heteroaryl moieties contain multiple substituents.

      These reactions may be employed in a linear sequence

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to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes. Other reactions useful in the preparation of heteroaryl moieties are described in "Comprehensive 5 Organic Chemistry, Volume 4: Heterocyclic Compounds" ed. P.G. Sammes, Oxford (1979) and references therein. Aryl-aryl coupling is generally described in "Comprehensive Organic Functional Group Transformations," Katritzky et al. eds., pp 472-473, Pergamon Press (1995).

10

Synopsis of Schemes 1-22:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. Schemes 1- 13 illustrate synthesis of the instant aryl- 15 heteroaryl compound which incorporate a preferred benzylimidazolyl sidechain. Thus, in Scheme 1, for example, a arylheteroaryl intermediate that is not commercially available may be synthesized by methods known in the art. Thus, a suitably substituted heteroaryl boronic acid, such as a suitably substituted thiienyl boronic acid I may 20 be reacted under Suzuki coupling conditions (*Pure Appl. Chem.*, 63:419 (1991)) with a suitably substituted halogenated benzoic acid, such as 4-iodobenzoic acid, to provide the arylheteroaryl carboxylic acid II. The acid may be reduced and the triflate of the intermediate alcohol III may be formed in situ and coupled to a suitably substituted benzylimidazolyl 25 IV to provide, after deprotection, the instant compound V.

Schemes 2-5 illustrate other methods of synthesizing the key alcohol intermediates, which can then be processed as described in Scheme 1. Thus, Scheme 2 illustrates the analogous series of arylheteroaryl alcohol forming reactions starting with the halogenated 30 arylaldehyde.

Scheme 3 illustrates the reaction wherein the "terminal" 5-membered heteroaryl moiety is employed in the Suzuki coupling as the halogenated reactant. Such a coupling reaction is also compatible

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when one of the reactants incorporates a suitably protected hydroxyl functionality as illustrated in Scheme 4.

Negishi chemistry (*Org. Synth.*, 66:67 (1988)) may also be employed to form the arylheteroaryl component of the instant 5 compounds, as shown in Scheme 5. Thus, a suitably substituted zinc bromide adduct may be coupled to a suitably substituted phenyl halide in the presence of nickel (II) to provide the arylheteroaryl VII. The heteroaryl halide and the zinc bromide adduct may be selected based on the availability of the starting reagents.

10 Scheme 6 illustrates the utilization of a suitably substituted arylheteroaryl methyl bromide in the reaction with the protected imidazole as described in Scheme 1.

15 As illustrated in Scheme 7, the sequence of coupling reactions may be modified such that the phenyl-heteroaryl bond is formed last. Thus, a suitably substituted imidazole may first be alkylated with a suitably substituted benzyl halide to provide intermediate VIII. Intermediate VIII can then undergo Suzuki type coupling to a suitably substituted heteroaryl boronic acid.

20 Scheme 8 illustrates synthesis of an instant compound wherein a non-hydrogen R<sup>9b</sup> is incorporated in the preferred W moiety, imidazolyl. Thus, a readily available 4-substituted imidazole IX may be selectively iodinated to provide the 5-iodoimidazole X. That imidazole may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate XI. Intermediate XI can then 25 undergo the alkylation reactions that were described hereinabove.

30 Scheme 9 illustrates synthesis of instant compounds that incorporate a preferred imidazolyl moiety connected to the arylheteroaryl via an alkyl amino, sulfonamide or amide linker. Thus, the 4-aminoalkylimidazole XII, wherein the primary amine is protected as the phthalimide, is selectively alkylated then deprotected to provide the amine XIII. The amine XIII may then react under conditions well known in the art with various activated arylheteroaryl moieties to provide the instant compounds shown.

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Compounds of the instant invention wherein the  $A^1(CR^{1a}2)_nA^2(CR^{1a}2)_n$  linker is oxygen may be synthesized by methods known in the art, for example as shown in Scheme 10. The suitably substituted phenol XIV may be reacted with methyl 5 N-(cyano)methanimidate to provide the 4-phenoxyimidazole XV. After selective protection of one of the imidazolyl nitrogens, the intermediate XVI can undergo alkylation reactions as described for the benzylimidazoles hereinabove.

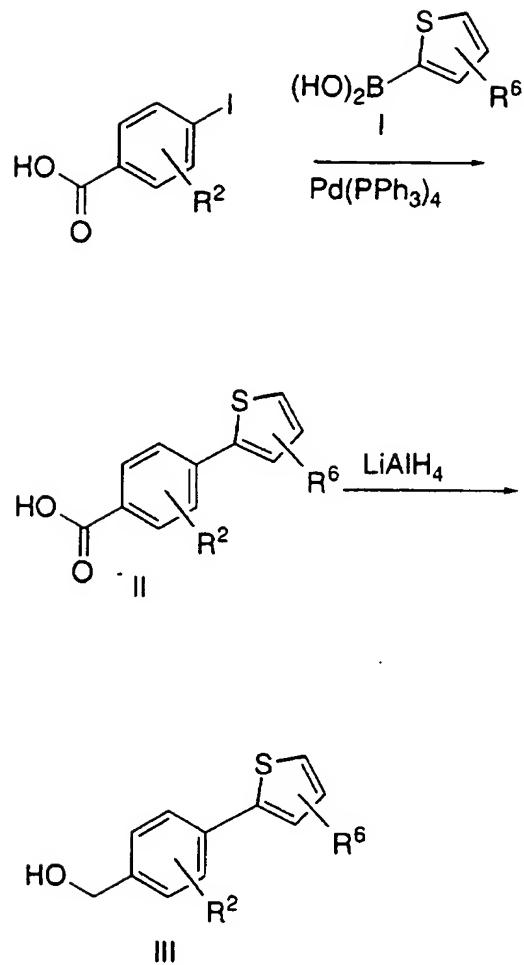
Scheme 11 illustrates an analogous series of reactions 10 wherein the  $(CR^{1b}2)_pX(CR^{1b}2)_p$  linker of the instant compounds is oxygen. Thus, a suitably substituted haloaryl alcohol, such as 4-bromophenol and the like, is reacted with methyl N-(cyano) methanimidate to provide intermediate XVI. Intermediate XVI is then protected and, if desired to form a compound of a preferred 15 embodiment, alkylated with a suitably protected benzyl. The intermediate XVII can then be coupled to a heteroaryl moiety by Suzuki chemistry to provide the instant compound.

Compounds of the instant invention wherein the  $A^1(CR^{1a}2)_nA^2(CR^{1a}2)_n$  linker is a substituted methylene may be 20 synthesized by the methods shown in Scheme 12. Thus, the N-protected imidazolyl iodide XVIII is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol XIX. Acylation, followed by the alkylation procedure illustrated in the Schemes above 25 (in particular, Scheme 1) provides the instant compound XX. If other  $R^{1a}$  substituents are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

Grignard chemistry may also be employed to form a substituted alkyl linker between the arylheteroaryl and the preferred W (imidazolyl) as shown in Scheme 13. Similar substituent manipulation 30 as shown in Scheme 12 may be performed on the fully functionalized compound which incorporates an  $R^{1b}$  hydroxyl moiety.

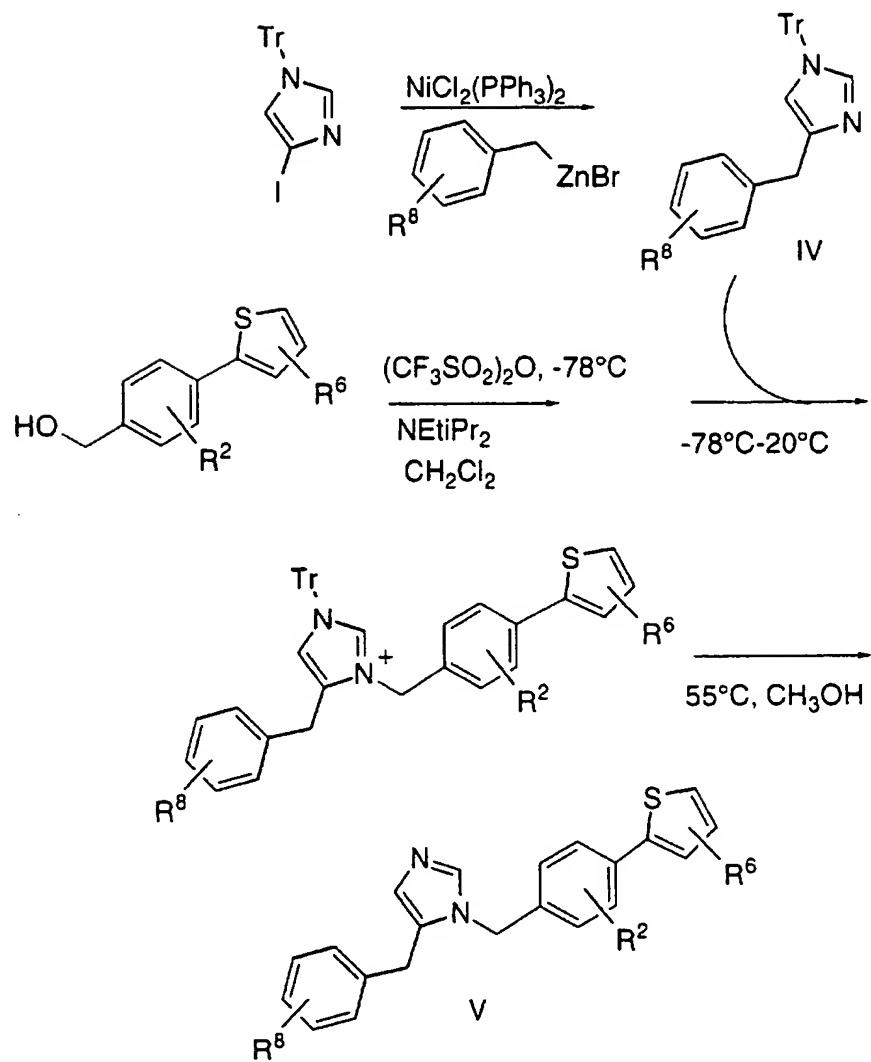
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SCHEME 1



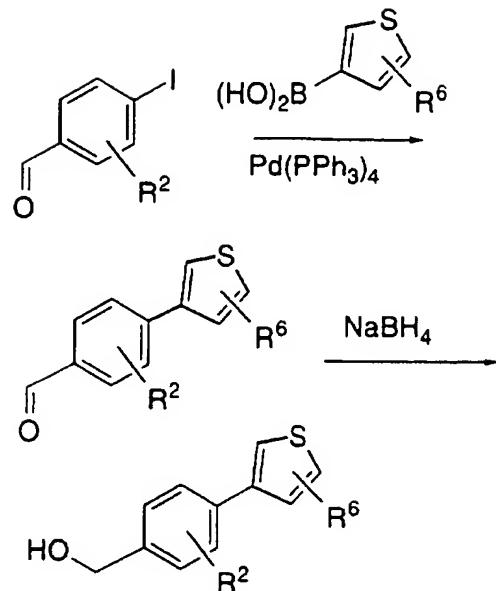
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## SCHEME 1 (continued)



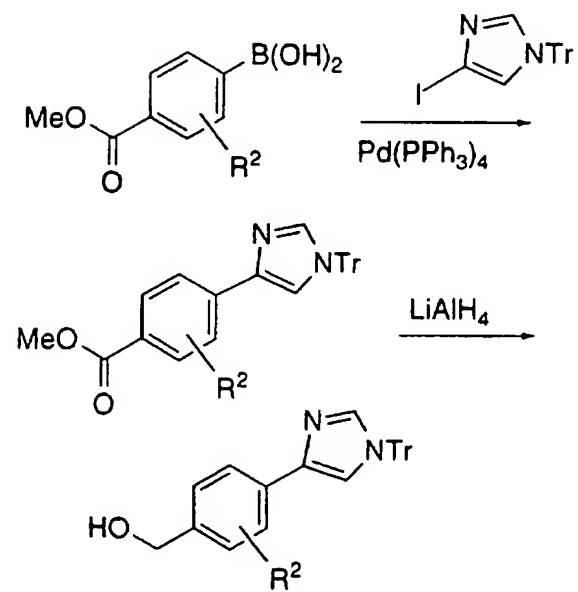
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SCHEME 2



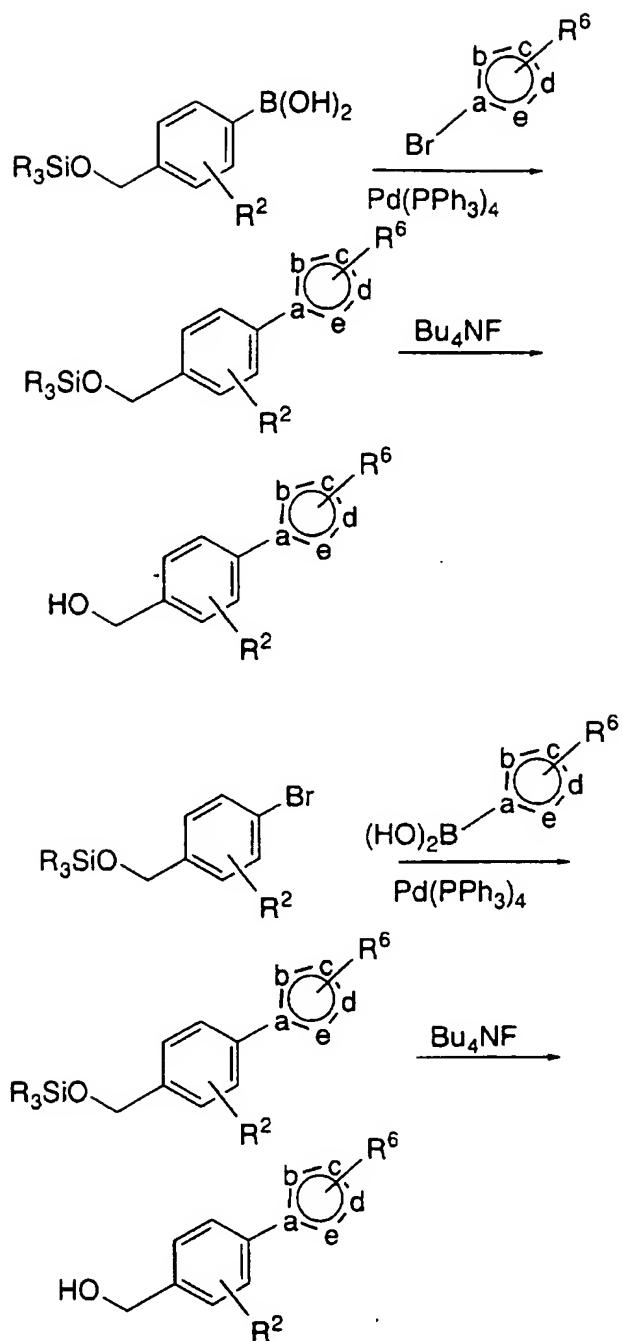
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SCHEME 3

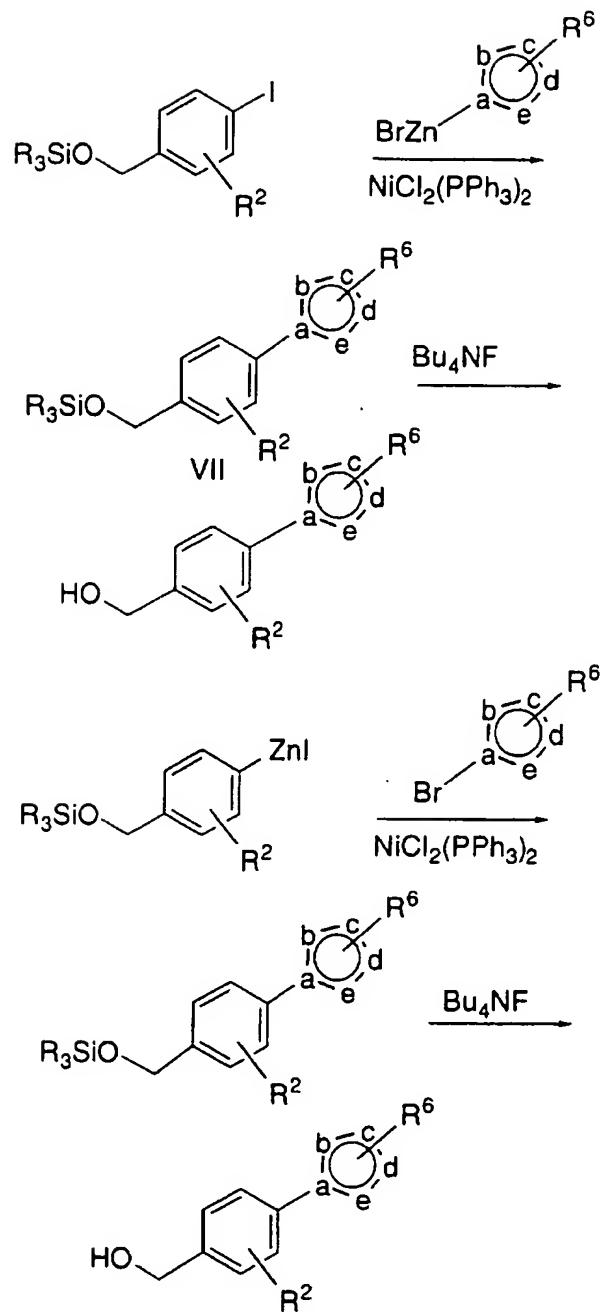


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SCHEME 4

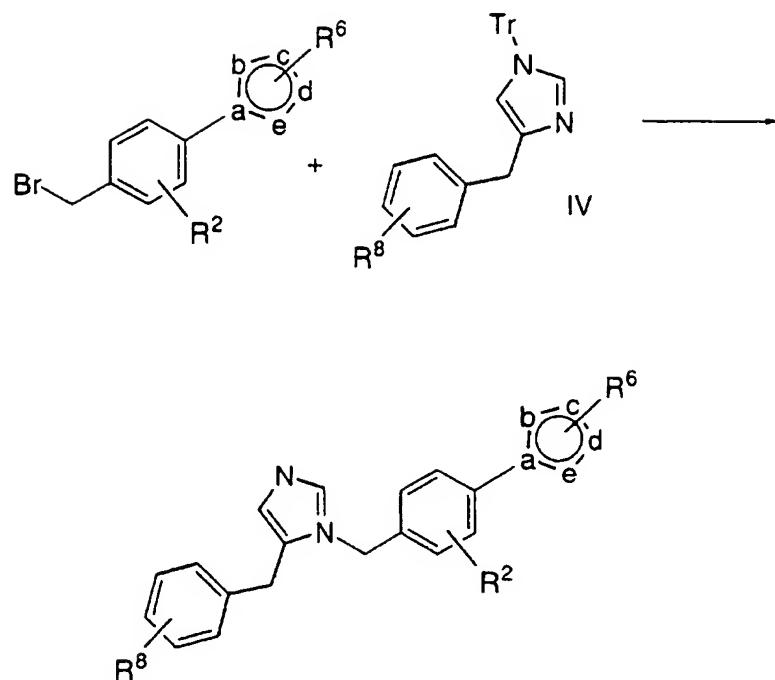


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SCHEME 5

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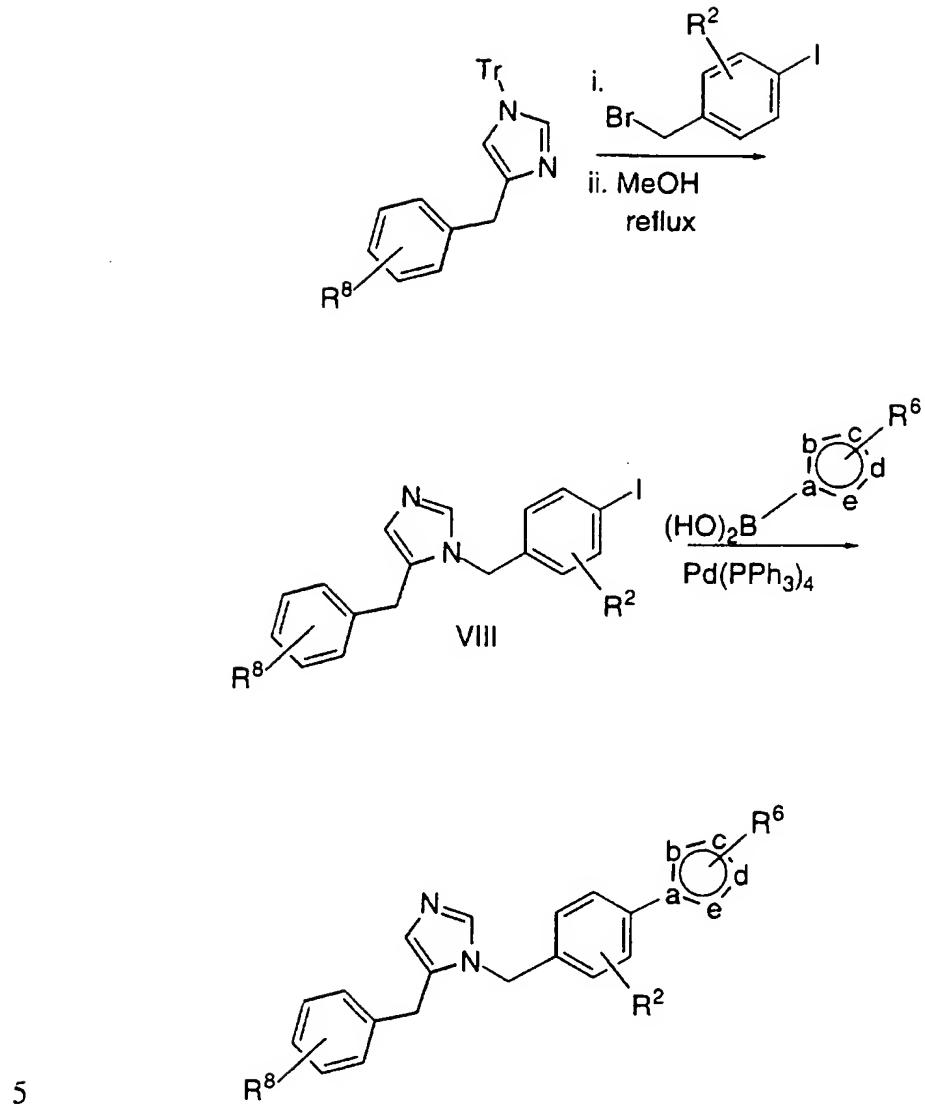
SCHEME 6



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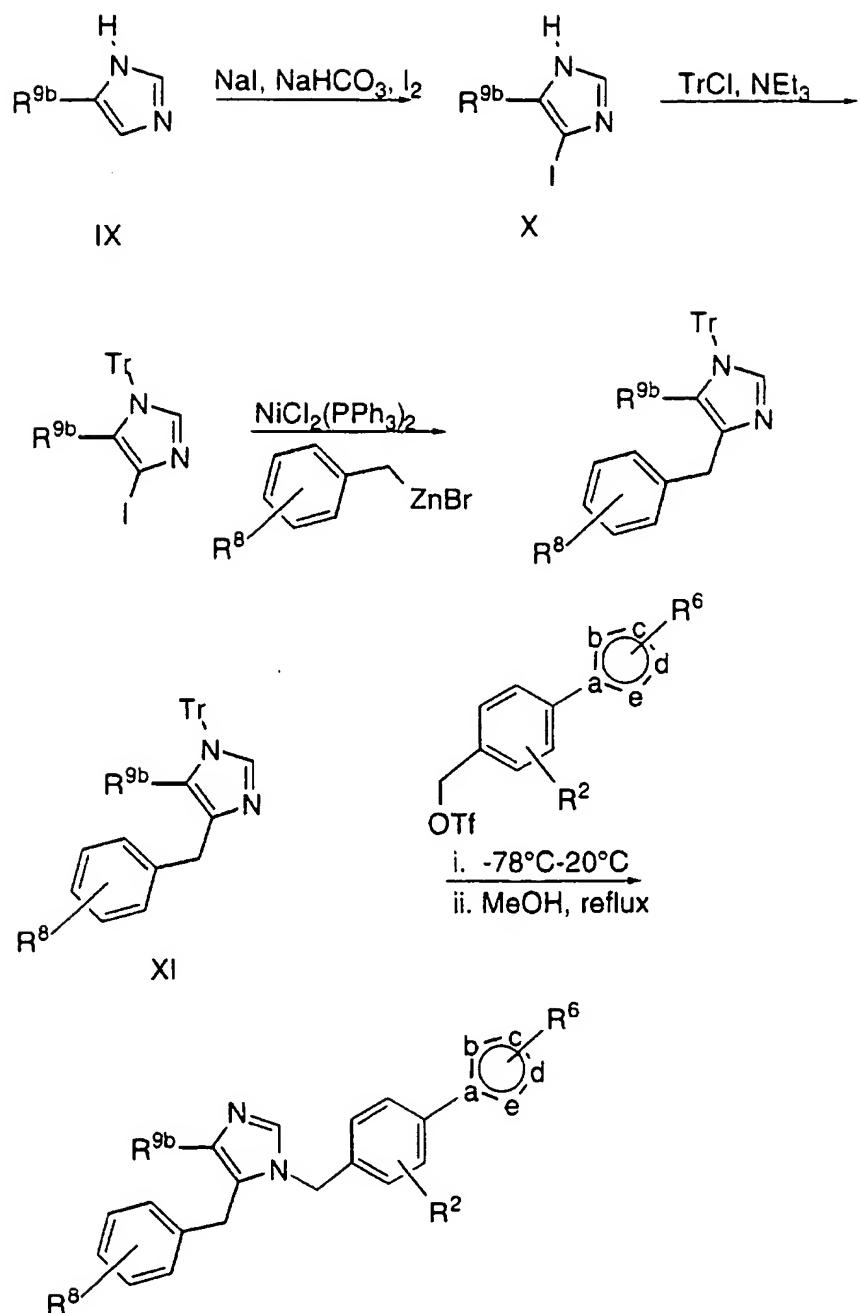
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SCHEME 7

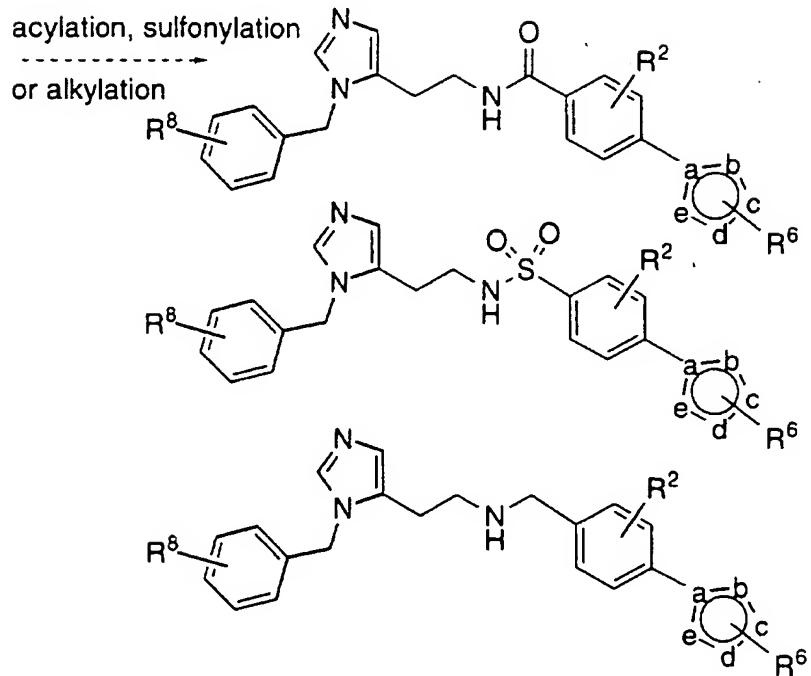
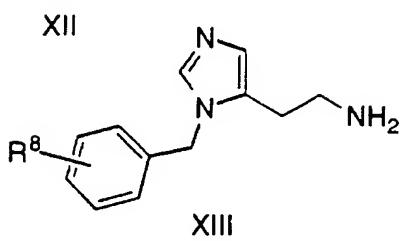
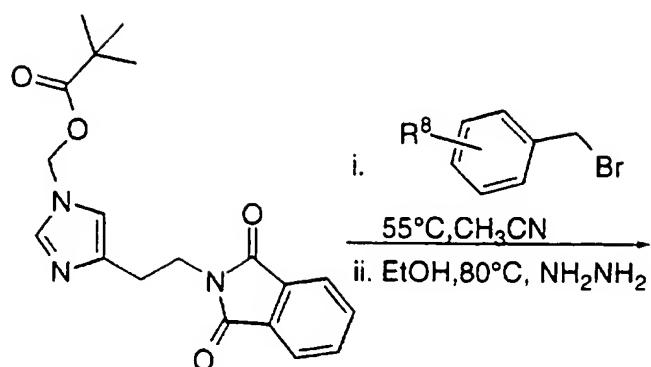


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SCHEME 8

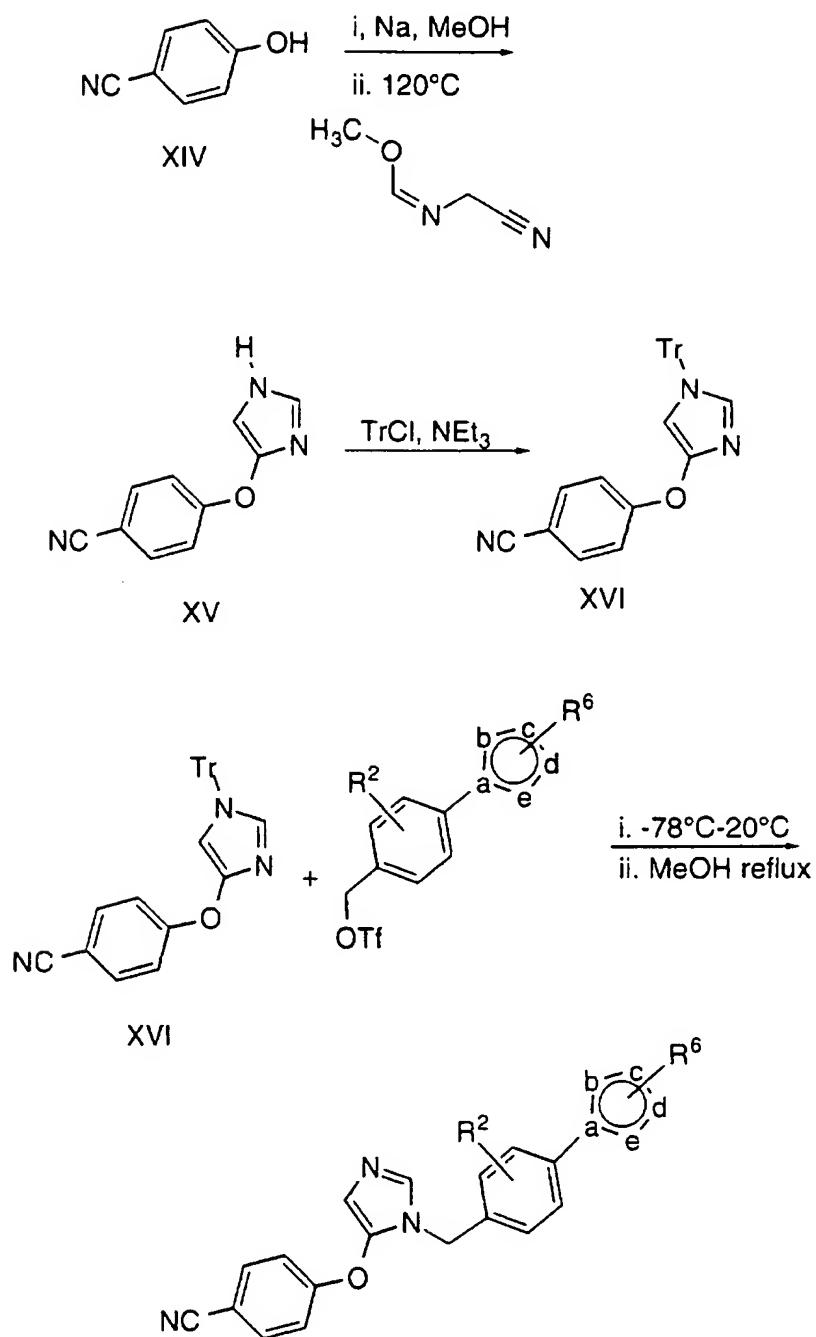


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SCHEME 9

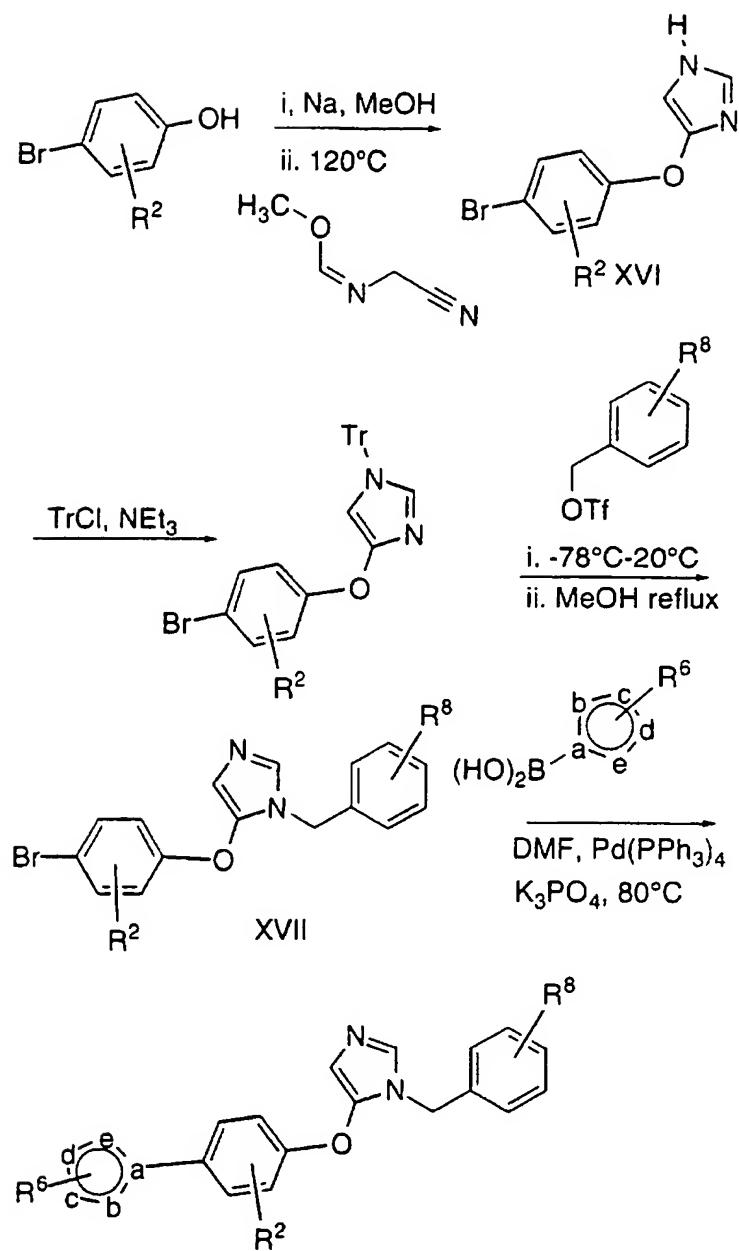
- 52 -

SCHEME 10



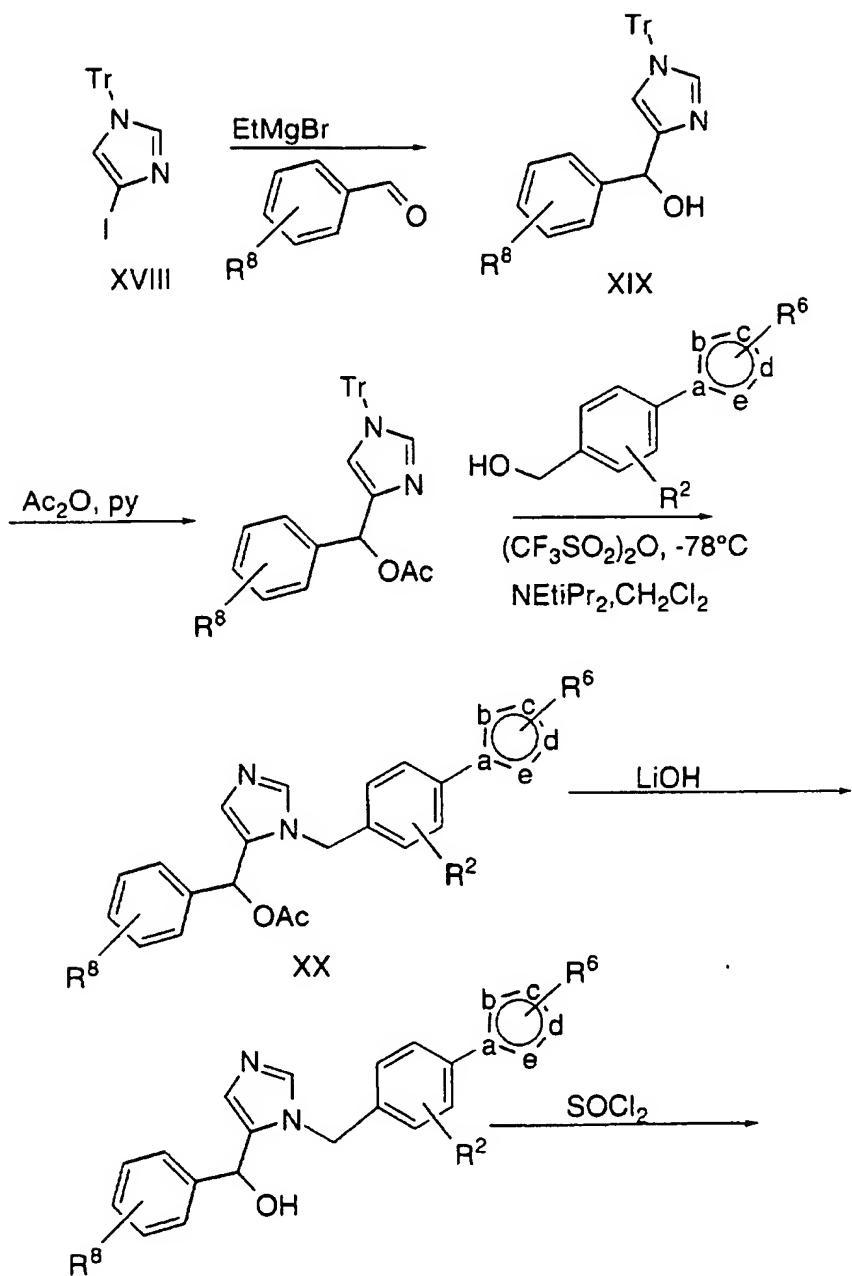
- 53 -

## SCHEME 11

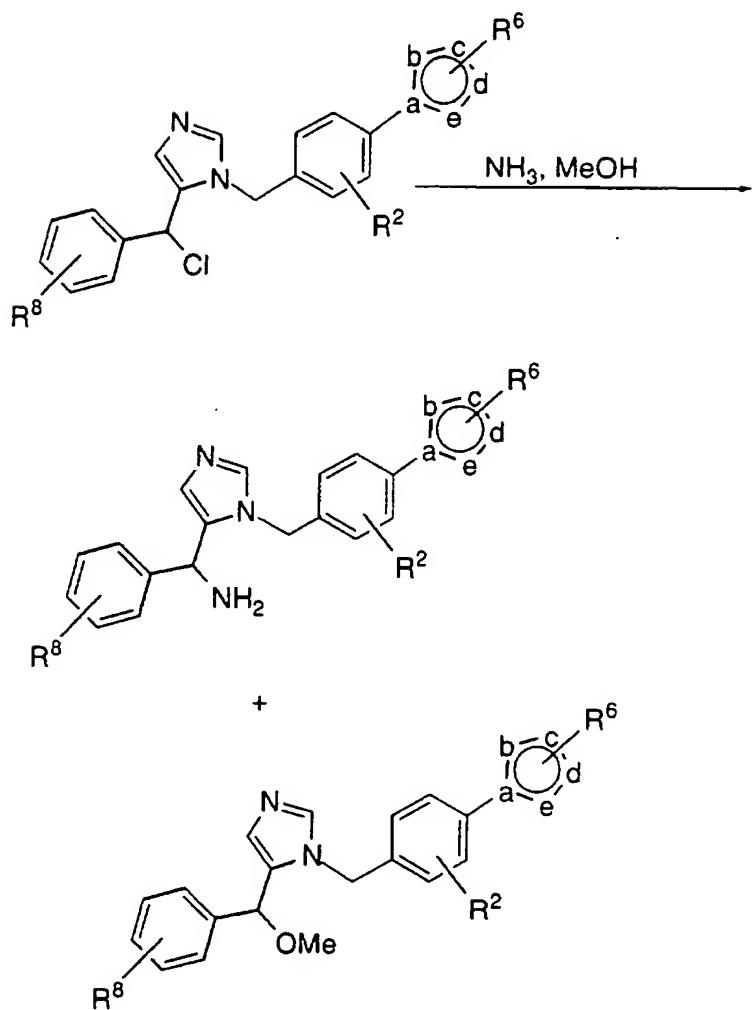


- 54 -

## SCHEME 12

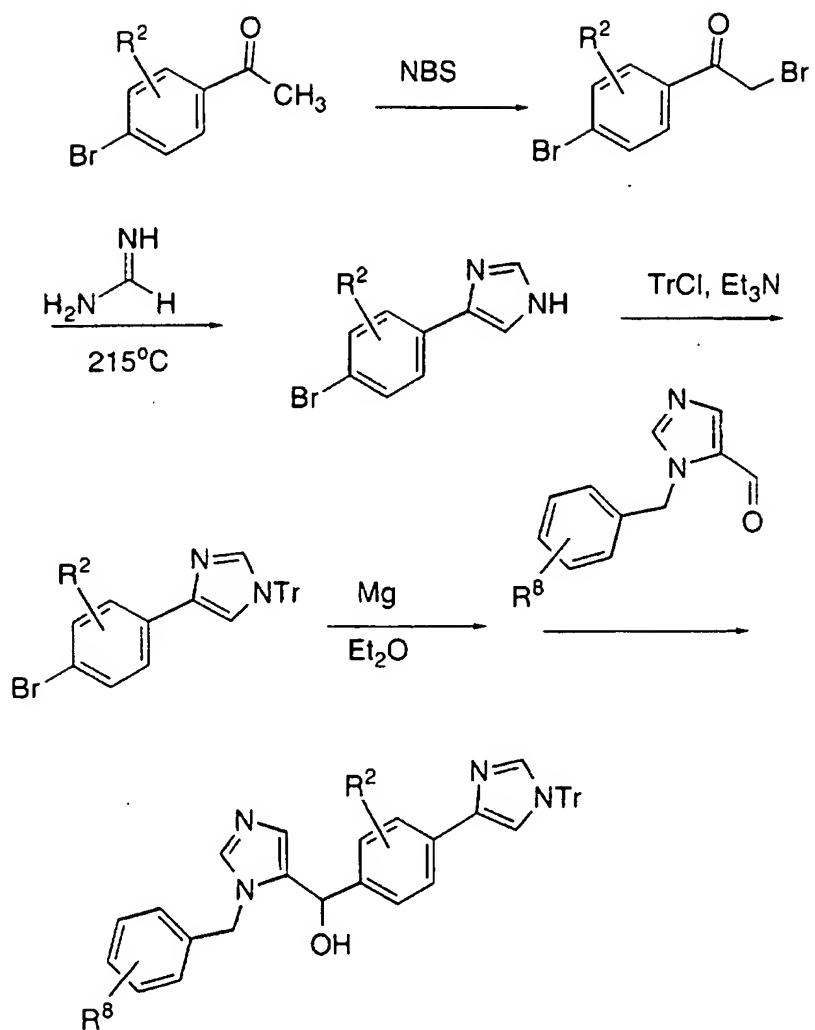


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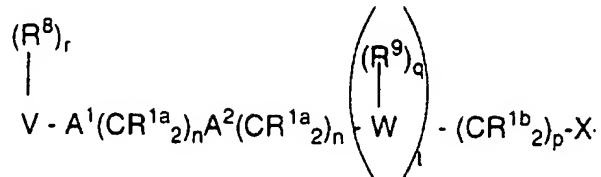
SCHEME 12 (continued)

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SCHEME 13



Schemes 14-22 illustrate reactions wherein the moiety



incorporated in the compounds of the instant invention is represented by other than a substituted imidazole-containing group.

5        Thus, the intermediates whose synthesis are illustrated in Schemes hereinabove and other arylheteroaryl intermediates obtained commercially or readily synthesized, can be coupled with a variety of aldehydes. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, 1988, 67, 69-75, from the appropriate amino acid. Grignard chemistry may be utilized, as shown in Scheme 14, to incorporate the arylheteroaryl moiety. Thus, a suitably substituted arylheteroaryl Grignard reagent is reacted with an aldehyde to provide the C-alkylated instant compound **XXI**. Compound **XXI**

10      can be deoxygenated by methods known in the art, such as a catalytic hydrogention, then deprotected with trifluoroacetic acid in methylene chloride to give the final compound **XXII**. The final product **XXII** may be isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine

15      **XXII** can further be selectively protected to obtain **XXIII**, which can subsequently be reductively alkylated with a second aldehyde to obtain **XXIV**. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole **XXV** can be accomplished by literature procedures.

20      25      If the arylheteroaryl subunit reagent is reacted with an aldehyde which also has a protected hydroxyl group, such as **XXVI** in Scheme 15, the protecting groups can be subsequently removed to unmask the hydroxyl group (Schemes 15, 16). The alcohol can be oxidized under standard conditions to e.g. an aldehyde, which can then

30      be reacted with a variety of organometallic reagents such as Grignard

reagents, to obtain secondary alcohols such as **XXX**. In addition, the fully deprotected amino alcohol **XXXI** can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as **XXXII** (Scheme 16), or tertiary amines.

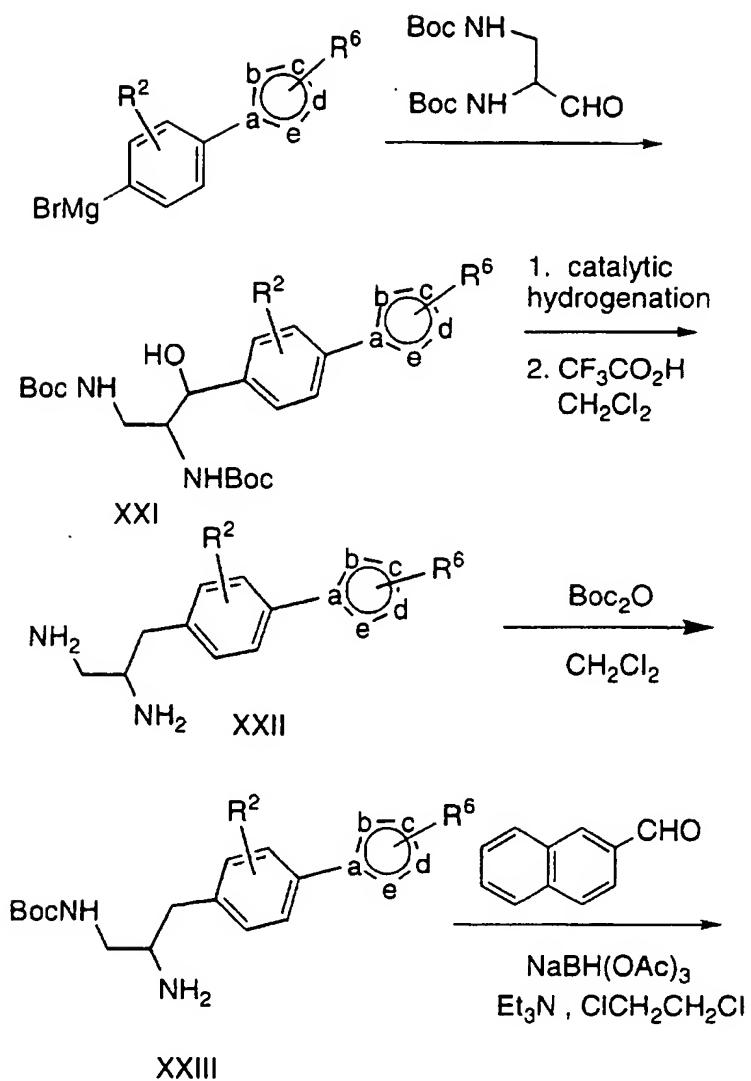
5 The Boc protected amino alcohol **XXVIII** can also be utilized to synthesize 2-aziridinylmethylarylhetereoaryl such as **XXXIII** (Scheme 17). Treating **XXVIII** with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide led to the 10 formation of aziridine **XXXIII**. The aziridine is reacted with a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product **XXXIV**.

15 In addition, the arylhetereoaryl subunit reagent can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as **XL**, as shown in Scheme 18. When R' is an aryl group, **XL** can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce **XLI**. Alternatively, the amine protecting group in **XL** can be removed, and O-alkylated phenolic amines such as **XLII** 20 produced.

25 Schemes 19-22 illustrate syntheses of suitably substituted aldehydes useful in the syntheses of the instant compounds wherein the variable W is present as a pyridyl moiety. Similar synthetic strategies for preparing alkanols that incorporate other heterocyclic moieties for variable W are also well known in the art.

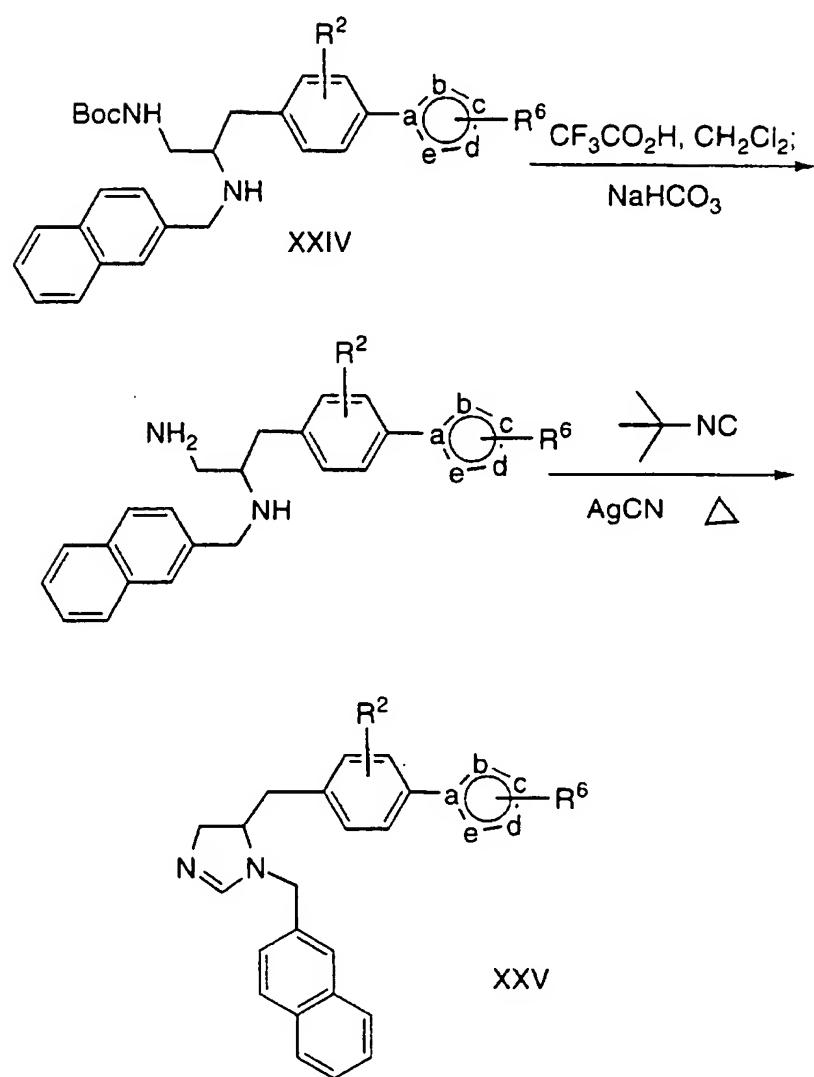
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## SCHEME 14



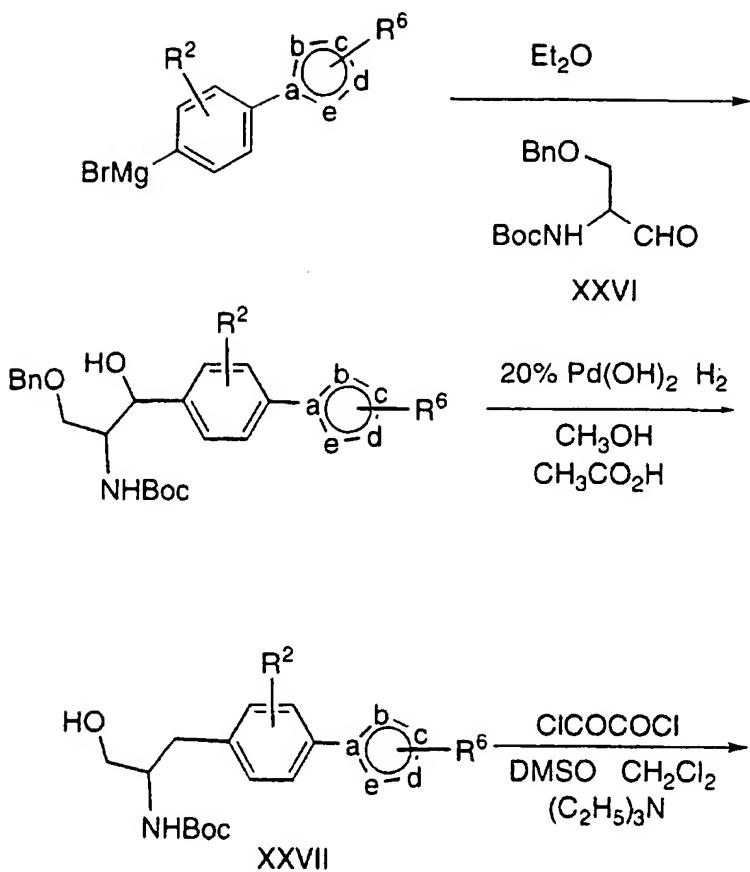
- 60 -

SCHEME 14 (continued)



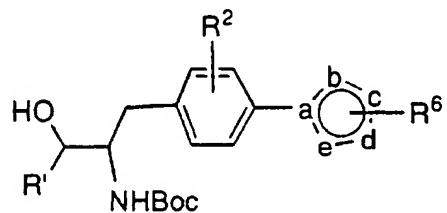
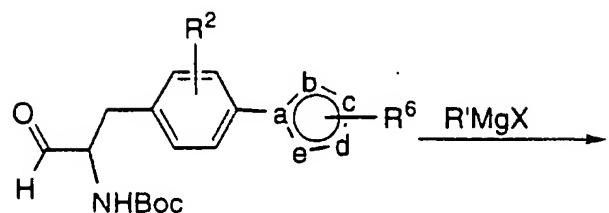
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## SCHEME 15



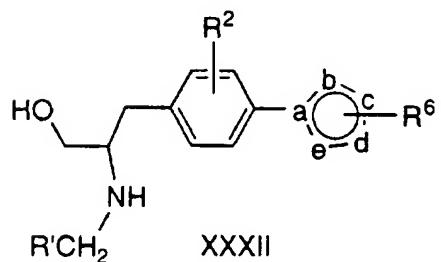
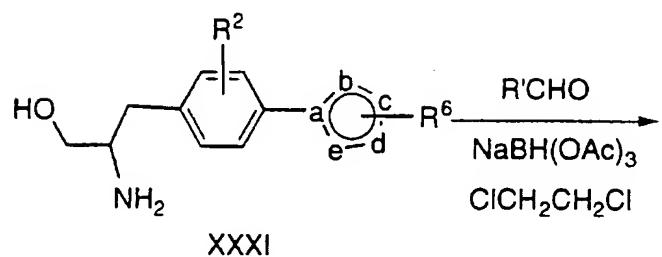
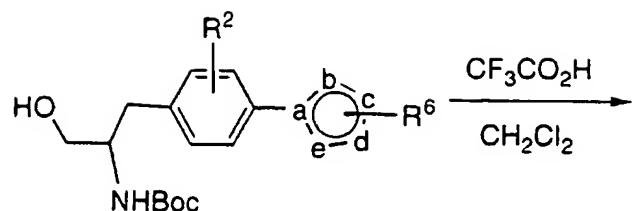
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SCHEME 15 (continued)



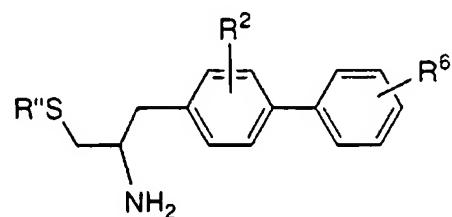
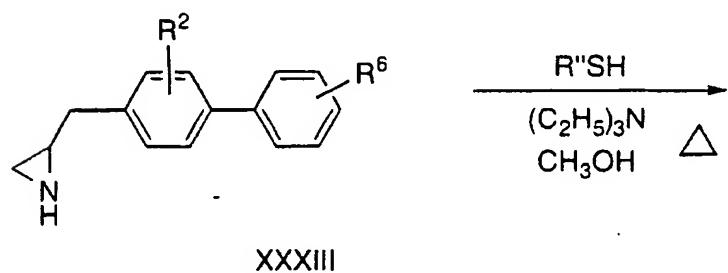
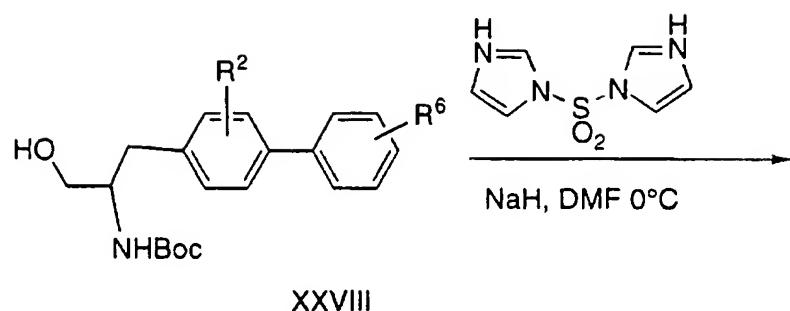
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SCHEME 16



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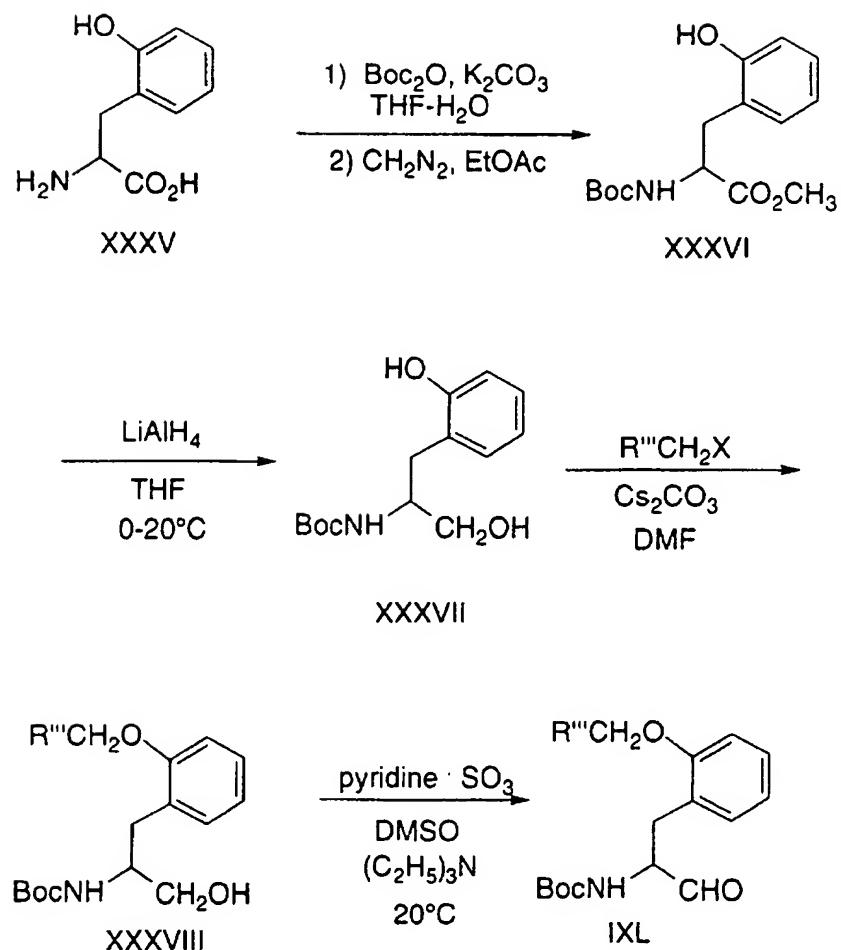
SCHEME 17



XXXIV

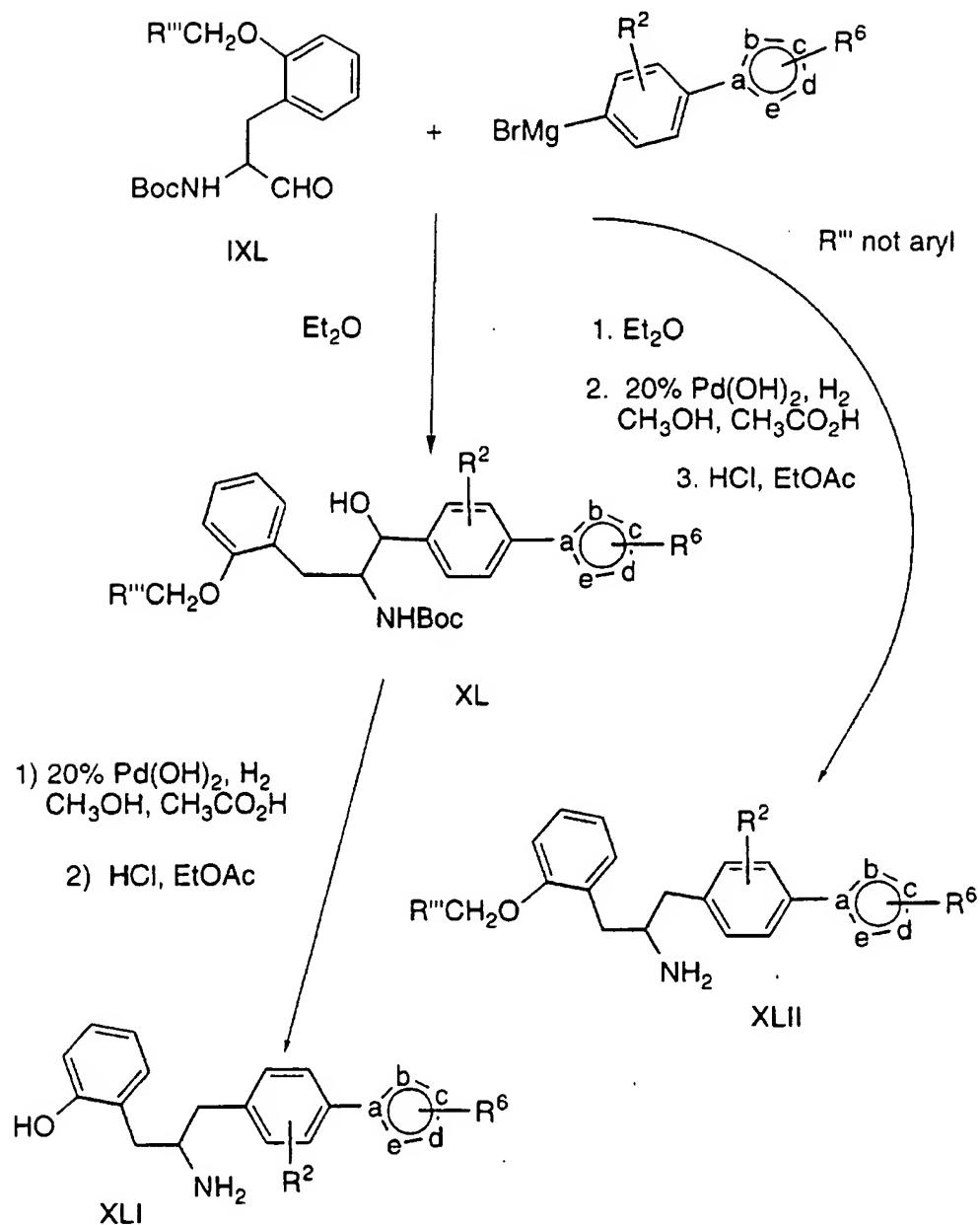
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SCHEME 18



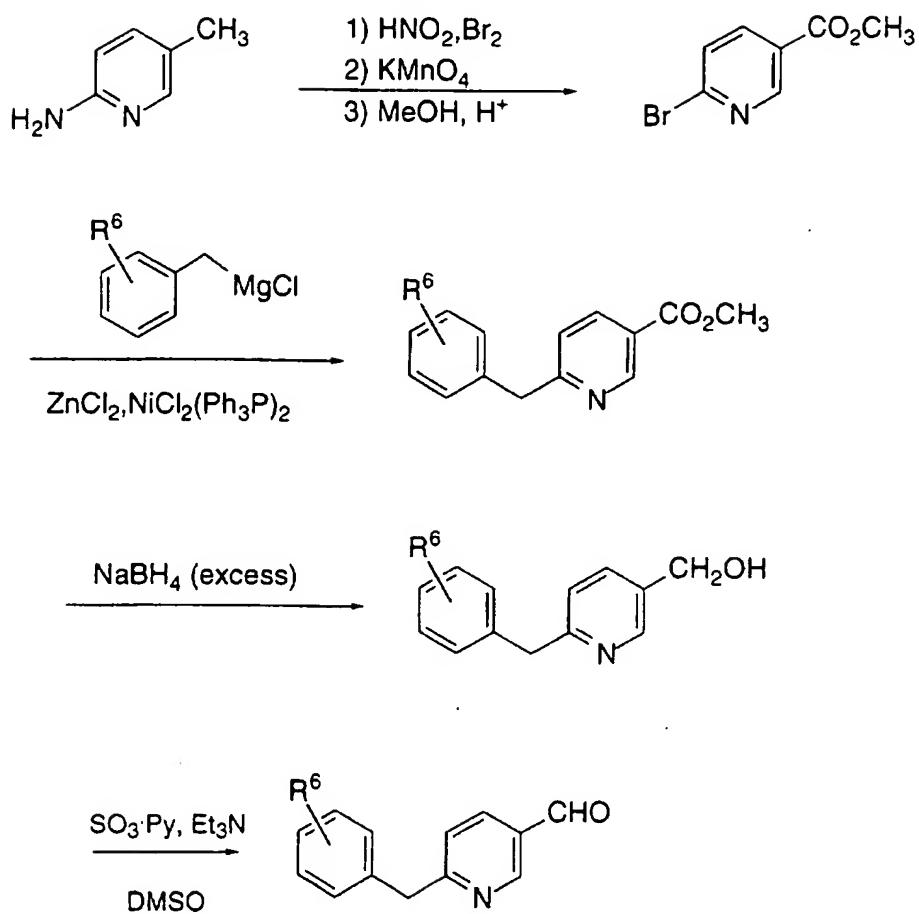
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## SCHEME 18 (continued)



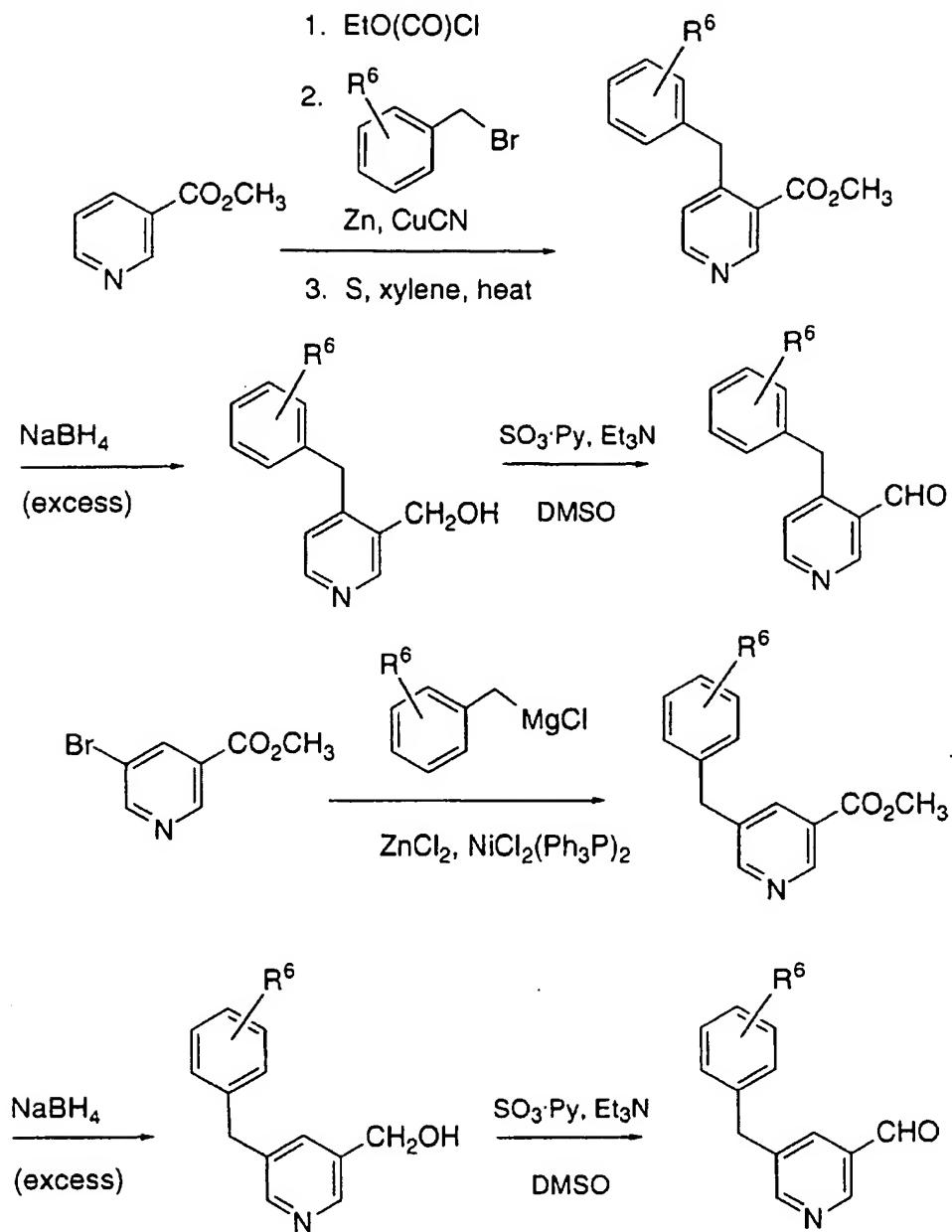
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SCHEME 19



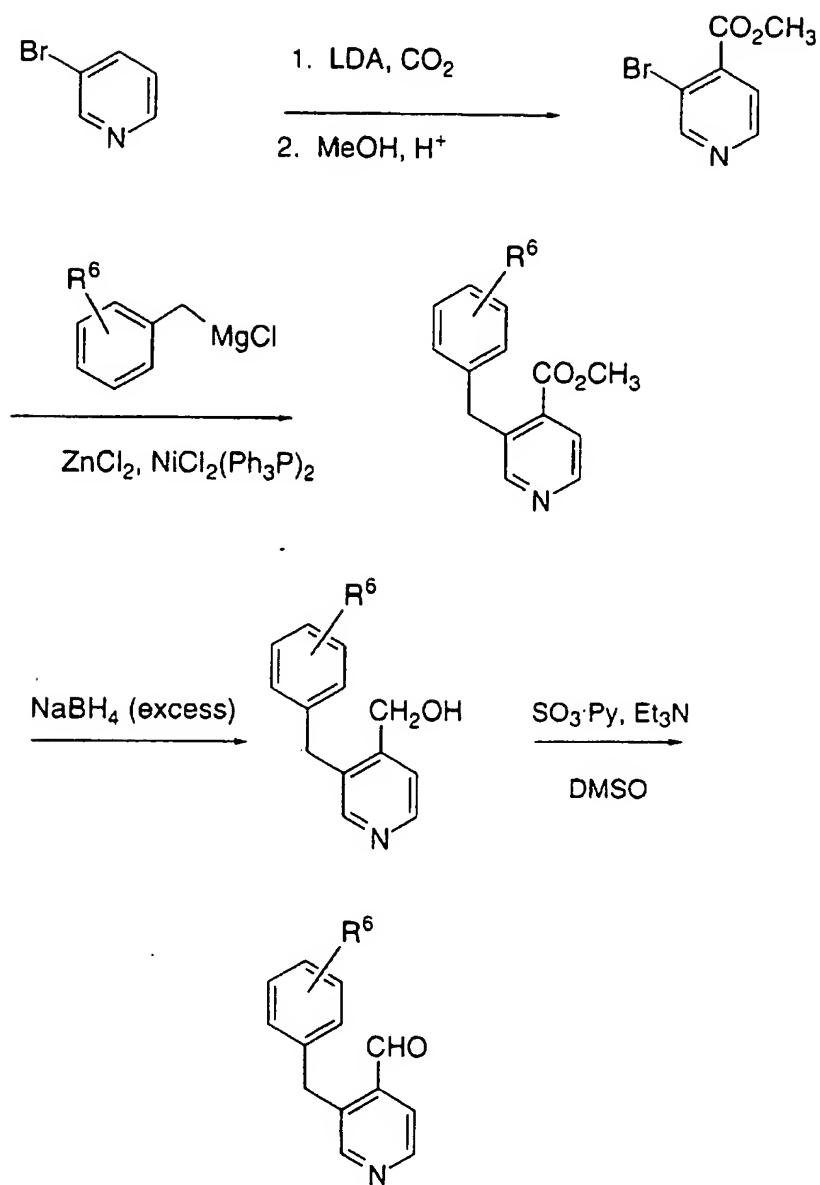
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SCHEME 20



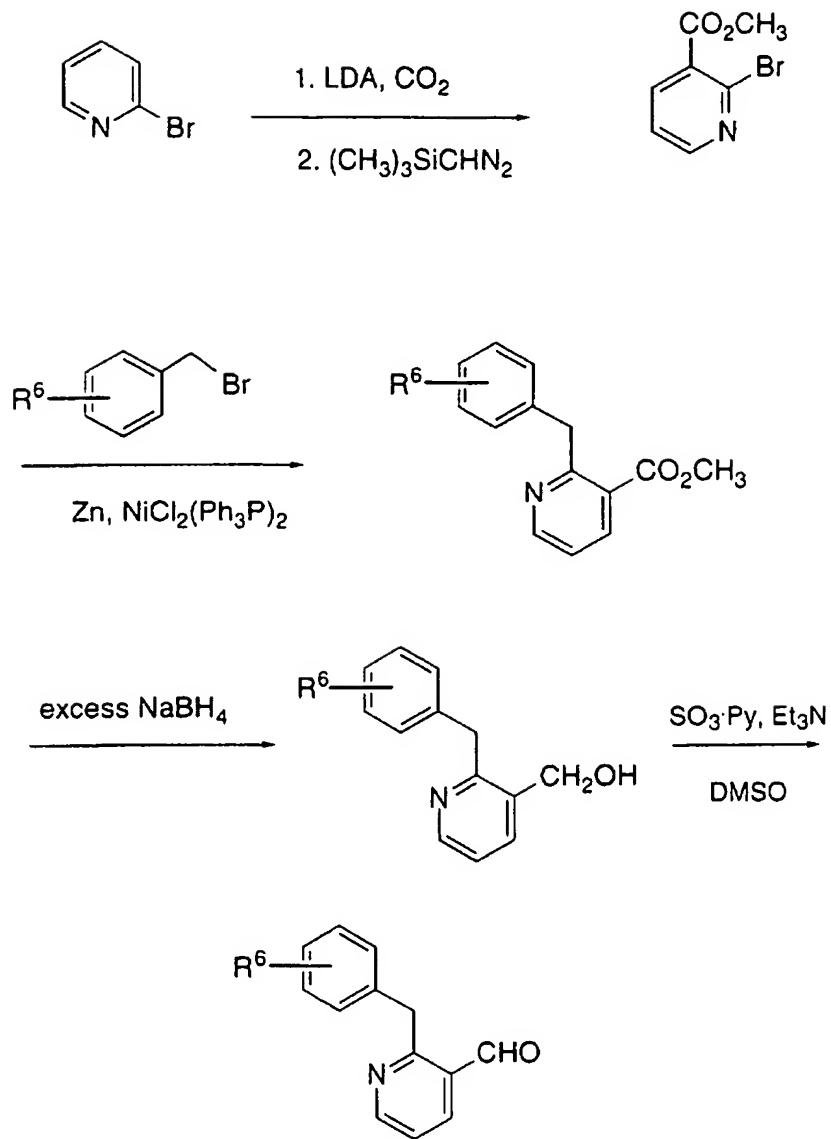
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SCHEME 21



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SCHEME 22



5

The instant compounds are useful as pharmaceutical agents for mammals, especially for humans. These compounds may be administered to patients for use in the treatment of cancer. Examples of the type of cancer which may be treated with the compounds of this

invention include, but are not limited to, colorectal carcinoma, exocrine pancreatic carcinoma, myeloid leukemias and neurological tumors. Such tumors may arise by mutations in the *ras* genes themselves, mutations in the proteins that can regulate Ras activity (i.e., neurofibromin (NF-1), *neu*, *scr*, *abl*, *lck*, *fyn*) or by other mechanisms.

5 The compounds of the instant invention inhibit farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. The instant compounds may also inhibit tumor angiogenesis, thereby affecting the growth of tumors (J. Rak et al. *Cancer Research*, 10 55:4575-4580 (1995)). Such anti-angiogenesis properties of the instant compounds may also be useful in the treatment of certain forms of blindness related to retinal vascularization.

15 The compounds of this invention are also useful for inhibiting other proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes (i.e., the Ras gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished by the administration of an effective amount of the compounds of the invention to a mammal in need of such treatment. For example, a 20 component of NF-1 is a benign proliferative disorder.

25 The instant compounds may also be useful in the treatment of certain viral infections, in particular in the treatment of hepatitis delta and related viruses (J.S. Glenn et al. *Science*, 256:1331-1333 (1992)).

30 The compounds of the instant invention are also useful in the prevention of restenosis after percutaneous transluminal coronary angioplasty by inhibiting neointimal formation (C. Indolfi et al. *Nature medicine*, 1:541-545(1995)).

35 The instant compounds may also be useful in the treatment and prevention of polycystic kidney disease (D.L. Schaffner et al. *American Journal of Pathology*, 142:1051-1060 (1993) and B. Cowley, Jr. et al. *FASEB Journal*, 2:A3160 (1988)).

The instant compounds may also be useful for the treatment of fungal infections.

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The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical 5 composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use of a chemotherapeutic compound according 10 to this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral 15 administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, 20 sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The compounds of the instant invention may also be 25 co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. For example, the instant compounds may be useful in combination with known anti-cancer and cytotoxic agents. Similarly, the instant compounds may be useful in combination with agents that are 30 effective in the treatment and prevention of NF-1, restinosis, polycystic kidney disease, infections of hepatitis delta and related viruses and fungal infections.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range

described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

5 The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous  
10 10 solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's blood-stream by local bolus injection.

15 As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific amounts, as well as any product which results, directly or indirectly, from combination of the specific ingredients in the specified amounts.

20 20 When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

25 In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

30 The compounds of the instant invention are also useful as a component in an assay to rapidly determine the presence and quantity of farnesyl-protein transferase (FPTase) in a composition. Thus the composition to be tested may be divided and the two portions contacted with mixtures which comprise a known substrate

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of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate and, in one of the mixtures, a compound of the instant invention. After the assay mixtures are incubated for an sufficient period of time, well known in the art, 5 to allow the FPTase to farnesylyate the substrate, the chemical content of the assay mixtures may be determined by well known immuno-logical, radiochemical or chromatographic techniques. Because the compounds of the instant invention are selective inhibitors of FPTase, absence or quantitative reduction of the amount of substrate 10 in the assay mixture without the compound of the instant invention relative to the presence of the unchanged substrate in the assay containing the instant compound is indicative of the presence of FPTase in the composition to be tested.

It would be readily apparent to one of ordinary skill 15 in the art that such an assay as described above would be useful in identifying tissue samples which contain farnesyl-protein transferase and quantitating the enzyme. Thus, potent inhibitor compounds of the instant invention may be used in an active site titration assay to determine the quantity of enzyme in the sample. A series of samples 20 composed of aliquots of a tissue extract containing an unknown amount of farnesyl-protein transferase, an excess amount of a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate are incubated for an appropriate period of time in the presence of varying concentrations of a compound 25 of the instant invention. The concentration of a sufficiently potent inhibitor (i.e., one that has a  $K_i$  substantially smaller than the concentration of enzyme in the assay vessel) required to inhibit the enzymatic activity of the sample by 50% is approximately equal to half of the concentration of the enzyme in that particular sample.

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### EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

#### EXAMPLE 1

10 1-(4-(1,2,3-Thiadiazolyl)-phenylmethyl)-5-(4-cyanobenzyl)  
imidazole trifluoroacetate salt

---

Step A: 1-Trityl-4-(4-Cyanobenzyl)-imidazole

To a suspension of activated zinc dust (3.57g, 15 54.98mmol) in THF (50 mL) was added dibromoethane (0.315 mL, 3.60 mmol) and the reaction stirred for 45 minutes under argon at 20°C. The suspension was cooled to 0°C and  $\alpha$ -bromo-p-tolunitrile (9.33g, 47.6 mmol) in THF (100 mL) was added dropwise over a period of 10 minutes. The reaction was then allowed to stir at 20°C 20 for 6 hours and bis(triphenylphosphine)Nickel II chloride (2.40g, 3.64 mmol) and 4-iodo-1-tritylimidazole (15.95g, 36.6 mmol, S. V. Ley, et al., J. Org. Chem. 56, 5739 (1991)) was added in one portion. The resulting mixture was stirred 16 hours at 20°C and then quenched by addition of saturated NH<sub>4</sub>Cl solution (100 mL) 25 and the mixture stirred for 2 hours. Saturated aq. NaHCO<sub>3</sub> solution was added to give a pH of 8 and the solution was extracted with EtOAc (2 x 250 mL), dried, (MgSO<sub>4</sub>) and the solvent evaporated in vacuo. The residue was chromatographed (Silica gel, 0-20% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound as a white solid. 30 <sup>1</sup>H NMR (CDCl<sub>3</sub> 400MHz)  $\delta$  7.54 (2H, d, J=7.9Hz), 7.38(1H, s), 7.36-7.29 (11H, m), 7.15-7.09(6H, m), 6.58(1H, s) and 3.93(2H, s) ppm.

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Step B: 1-(4-(1,2,3-Thiadiazolyl)-phenylmethyl)-5-(4-cyanobenzyl) imidazole trifluoroacetate salt

To 1-Trityl-4-(4-Cyanobenzyl)-imidazole (199 mg, 0.468 mmol) in acetonitrile (1 mL) was added 4-(4-bromomethyl-phenyl)-1,2,3-thiadiazole (122 mg, 0.478 mmol) and the mixture heated at 55°C for 16 hours. The residue was dissolved in methanol (10 mL) and heated at reflux for 30 minutes, cooled and evaporated to dryness. The residue was partitioned between sat. aq. NaHCO<sub>3</sub> solution and CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was dried, (NaSO<sub>4</sub>) and the solvent evaporated in vacuo. The residue was chromatographed (silica gel, 3% methanol in CH<sub>2</sub>Cl<sub>2</sub>) and further purified by preparative HPLC, (gradient elution, 95 :5 to 5:95% water:acetonitrile containing 0.1% trifluoroacetic acid) to afford the title compound.

15 FAB MS 358(MH<sup>+</sup>)  
<sup>1</sup>H NMR (CD<sub>3</sub>OD 400MHz) δ 9.28(1H, s), 9.08(1H, d, J=1.5Hz), 8.04(2H, d, J=8.4Hz), 7.55(2H, d, J=8.4Hz), 7.44(1H, s), 7.27(2H, d, J=8.4Hz), 7.26(2H, d, J=8.4Hz), 5.47(2H, s) and 4.18(2H, s) ppm.

20

EXAMPLE 2

1-(4-[Thien-3-yl]phenylmethyl)-5-(4-cyanobenzyl)imidazole hydrochloride salt

25 Step A: Methyl (4-thien-3-yl)benzoate

A mixture of methyl 4-iodobenzoate(0.451 g, 1.72 mmol), 3-thienylboronic acid (1.56 g, 12.79 mmol), barium hydroxide (0.813 mg, 2.58 mmol), DME (8 mL) and water (1.5 mL) was purged with dry argon. Tetrakis(triphenyl-phosphine) palladium(0) (99.0 mg, 0.086 mmol) was added, and the resultant solution was stirred at 80 °C for 4 hours. The solvents were evaporated in vacuo, and the residue partitioned between EtOAc and water and acidified with 1M aq. HCl. The aqueous extract was separated, and extracted with EtOAc. The organic extracts

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were combined, washed with sat. aq. NaHCO<sub>3</sub> and 5% aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, dried, (Na<sub>2</sub>SO<sub>4</sub>) filtered and the solvent evaporated in vacuo. The residue was purified by chromatography (Silica gel, CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound.

5      <sup>1</sup>H NMR (CDCl<sub>3</sub> 400MHz) δ 8.06(2H, d, J=8.4Hz), 7.67(2H, d, J=8.4Hz), 7.57(1H, dd, J=1.6 and 2.8Hz), 7.45-7.40(2H, m) and 3.93(3H, s) ppm.

Step B:      4-Thien-3-yl-benzyl alcohol

10      To a solution of methyl (4-thien-3-yl)benzoate (552 g, 1.60 mmol) in THF (5 mL) at 0°C was added 1.0 M lithium aluminum hydride in diethyl ether (1.60 mL, 1.60 mmol) over 10 minutes. The reaction was allowed to stir at ambient temperature for 3 hours, cooled to 0°C, and quenched by dropwise addition of 15      water (0.10 mL), 4 N aq. NaOH (0.10 mL), and water (0.30 mL). The reaction was filtered through a pad of Celite and the filtrate evaporated in vacuo. The title compound was obtained as an oil and was used without further purification.

15      <sup>1</sup>H NMR (CDCl<sub>3</sub> 400MHz) δ 7.60(2H, d, J=8.2Hz), 7.46(1H, t, J=2.2Hz), 7.44-7.36(3H, m), 7.30-7.23(1H, m), 4.72(2H, d, J=5.9Hz) and 1.63(1H, t, J=5.9Hz) ppm.

Step C:      1-(4-[Thien-3-yl]phenylmethyl)-5-(4-cyanobenzyl)imidazole hydrochloride salt

25      To a solution of 4-thien-3-yl-benzyl alcohol (253 mg, 1.33 mmol) and diisopropylethylamine (0.464 mL, 2.66 mmol) in dichloromethane (7 mL) at -78°C was added trifluoromethane-sulfonic anhydride (0.224 mL, 1.33 mmol) and the mixture stirred at -78°C for 1 hour. To this mixture was added a solution of 30      1-trityl-4-(4-cyanobenzyl)-imidazole (566mg, 1.33 mmol) in dichloromethane (5 mL). The mixture was allowed to warm to ambient temperature and stirred for 2 hours. The solvent was evaporated in vacuo. The residue was dissolved in methanol (50 mL), heated at reflux for 1 hour, and the solvent evaporated in

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vacuo. The residue was partitioned between dichloromethane and sat. aq. NaHCO<sub>3</sub> solution. The organic layer was dried, (Na<sub>2</sub>SO<sub>4</sub>) and the solvent evaporated in vacuo. The residue was chromatographed (silica gel, 2% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) and the amine was 5 converted to the HCl salt by treatment with 1.0M HCl in aqueous acetonitrile. Evaporation of the solvent in vacuo afforded the title compound as a white solid.

Anal. Calcd for C<sub>22</sub>H<sub>17</sub>SN<sub>3</sub>•1.00 HCl•0.40 EtOAc:

C, 66.36; H, 5.00; N, 9.84.

10 Found: C, 65.97; H, 4.64; N, 9.61.

FAB MS 356(MH<sup>+</sup>)

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400MHz) δ 9.00(1H, d, J=1.5Hz), 7.70-7.56(4H, m), 7.45(1H, dd, J=5.1 and 2.9Hz), 7.43(1H, dd, J=1.5 and 5.2Hz), 7.39(1H, s), 7.27(2H, d, J=8.4Hz), 7.16(2H, d, J=8.4Hz), 15 5.39(2H, s) and 4.16(2H, s) ppm.

EXAMPLE 3In vitro inhibition of ras farnesyl transferase

Assays of farnesyl-protein transferase. Partially purified bovine FPTase and Ras peptides (Ras-CVLS, Ras-CVIM and Ras-CAIL) were prepared as described by Schaber *et al.*, *J. Biol. Chem.* 265:14701-14704 (1990), Pompliano, *et al.*, *Biochemistry* 31:3800 (1992) and Gibbs *et al.*, *PNAS U.S.A.* 86:6630-6634 (1989), respectively. Bovine FPTase was assayed in a volume of 100  $\mu$ l containing 100 mM *N*-(2-hydroxy ethyl) piperazine-*N'*-(2-ethane sulfonic acid) (HEPES), pH 7.4, 5 mM MgCl<sub>2</sub>, 5 mM dithiothreitol (DTT), 100 nM [<sup>3</sup>H]-farnesyl diphosphate ([<sup>3</sup>H]-FPP; 740 CBq/mmol, New England Nuclear), 650 nM Ras-CVLS and 10  $\mu$ g/ml FPTase at 31°C for 60 min. Reactions were initiated with FPTase and stopped with 1 ml of 1.0 M HCl in ethanol. Precipitates were collected onto filter-mats using a TomTec Mach II cell harvester, washed with 100% ethanol, dried and counted in an LKB  $\beta$ -plate counter. The assay was linear with respect to both substrates, FPTase levels and time; less than 10% of the [<sup>3</sup>H]-FPP was utilized during the reaction period. Purified compounds were dissolved in 100% dimethyl sulfoxide (DMSO) and were diluted 20-fold into the assay. Percentage inhibition is measured by the amount of incorporation of radioactivity in the presence of the test compound when compared to the amount of incorporation in the absence of the test compound.

Human FPTase was prepared as described by Omer *et al.*, *Biochemistry* 32:5167-5176 (1993). Human FPTase activity was assayed as described above with the exception that 0.1% (w/v) polyethylene glycol 20,000, 10  $\mu$ M ZnCl<sub>2</sub> and 100 nM Ras-CVIM were added to the reaction mixture. Reactions were performed for 30 min., stopped with 100  $\mu$ l of 30% (v/v) trichloroacetic acid (TCA) in ethanol and processed as described above for the bovine enzyme.

The compounds of the instant invention described in the above Examples 1-2 were tested for inhibitory activity against human

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FPTase by the assay described above and were found to have IC<sub>50</sub> of ≤50 μM.

#### EXAMPLE 4

5

##### In vivo ras farnesylation assay

The cell line used in this assay is a v-ras line derived from either Rat1 or NIH3T3 cells, which expressed viral Ha-ras p21. The assay is performed essentially as described in DeClue, J.E. *et al.*, 10 Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75% confluence are treated with the test compound (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labelled in 3 ml methionine-free DMEM supplemented with 10% regular DMEM, 2% fetal bovine serum and 400 15 mCi[<sup>35</sup>S]methionine (1000 Ci/mmol). After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM MgCl<sub>2</sub>/1mM DTT/10 mg/ml aprotinin/2 mg/ml leupeptin/2 mg/ml antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at 100,000 x g for 45 min. Aliquots of lysates containing equal numbers 20 of acid-precipitable counts are brought to 1 ml with IP buffer (lysis buffer lacking DTT) and immunoprecipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. *et al.*, J. Virol. 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 ml of a 25% suspension of protein A-Sepharose coated with rabbit anti rat IgG 25 is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 nM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100/0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and 30 autoradiographed. The intensities of the bands corresponding to farnesylated and nonfarnesylated ras proteins are compared to determine the percent inhibition of farnesyl transfer to protein.

EXAMPLE 5In vivo growth inhibition assay

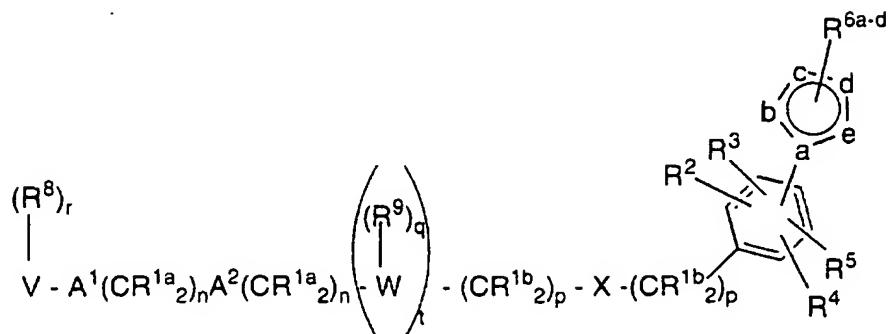
To determine the biological consequences of FPTase inhibition, the effect of the compounds of the instant invention on the anchorage-independent growth of Rat1 cells transformed with either a *v-ras*, *v-raf*, or *v-mos* oncogene is tested. Cells transformed by *v-Raf* and *v-Mos* maybe included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation.

Rat 1 cells transformed with either *v-ras*, *v-raf*, or *v-mos* are seeded at a density of  $1 \times 10^4$  cells per plate (35 mm in diameter) in a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an appropriate concentration of the instant compound (dissolved in methanol at 1000 times the final concentration used in the assay). The cells are fed twice weekly with 0.5 ml of medium A containing 0.1% methanol or the concentration of the instant compound. Photomicrographs are taken 16 days after the cultures are seeded and comparisons are made.

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WHAT IS CLAIMED IS:

1. A compound which inhibits farnesyl-protein transferase of the formula A:



5

A

wherein:

a is N or C;

10 from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH, O or S;

R<sup>1a</sup> and R<sup>1b</sup> are independently selected from:

- 15      a)    hydrogen,
- b)    aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, R<sup>11</sup>C(O)O-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- 20      c)    unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,

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$R^{10}O$ -,  $R^{11}S(O)m$ -,  $R^{10}C(O)NR^{10}$ -,  $(R^{10})_2NC(O)$ -,  
 $R^{10}_2N-C(NR^{10})$ -, CN,  $R^{10}C(O)$ -, N<sub>3</sub>, -N( $R^{10}$ )<sub>2</sub>, and  
 $R^{11}OC(O)-NR^{10}$ ;

5     $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are independently selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl,  $R^{12}O$ -,  
10     $R^{11}S(O)m$ -,  $R^{10}C(O)NR^{10}$ -,  $(R^{10})_2NC(O)$ -,  $R^{11}C(O)O$ -,  
 $R^{10}_2N-C(NR^{10})$ -, CN, NO<sub>2</sub>,  $R^{10}C(O)$ -, N<sub>3</sub>, -N( $R^{10}$ )<sub>2</sub>,  
or  $R^{11}OC(O)-NR^{10}$ ,
- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the  
15    substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,  $R^{12}O$ -,  $R^{11}S(O)m$ -,  $R^{10}C(O)NR^{10}$ -,  $(R^{10})_2NC(O)$ -,  
 $R^{10}_2N-C(NR^{10})$ -, CN,  $R^{10}C(O)$ -, N<sub>3</sub>, -N( $R^{10}$ )<sub>2</sub>, and  
20     $R^{11}OC(O)-NR^{10}$ ;

provided that when  $R^2$ ,  $R^3$ ,  $R^4$  or  $R^5$  is unsubstituted or substituted heterocycle, attachment of  $R^2$ ,  $R^3$ ,  $R^4$  or  $R^5$  to the phenyl ring is through a substitutable heterocycle ring carbon;

25

$R^{6a}$ ,  $R^{6b}$ ,  $R^{6c}$  and  $R^{6d}$  are independently selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl,  $R^{12}O$ -,  
30     $R^{11}S(O)m$ -,  $R^{10}C(O)NR^{10}$ -,  $(R^{10})_2NC(O)$ -,  $R^{11}C(O)O$ -,  
 $R^{10}_2N-C(NR^{10})$ -, CN, NO<sub>2</sub>,  $R^{10}C(O)$ -, N<sub>3</sub>, -N( $R^{10}$ )<sub>2</sub>,  
or  $R^{11}OC(O)-NR^{10}$ ,
- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,

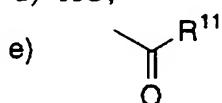
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5           d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

10           R<sup>7</sup> is selected from: H; C<sub>1</sub>-4 alkyl, C<sub>3</sub>-6 cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

15

a) C<sub>1</sub>-4 alkoxy,  
b) aryl or heterocycle,  
c) halogen,  
d) HO,



f) -SO<sub>2</sub>R<sup>11</sup>,  
g) N(R<sup>10</sup>)<sub>2</sub> or  
h) C<sub>1</sub>-4 perfluoroalkyl;

20           R<sup>8</sup> is independently selected from:

25

30

a) hydrogen,  
b) aryl, substituted aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, perfluoroalkyl, F, Cl, Br, R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and  
c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, perfluoroalkyl, F, Cl, Br, R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NH-, (R<sup>10</sup>)<sub>2</sub>NC(O)-,

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$R^{10}_2N-C(NR^{10})-$ , CN,  $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ , or  
 $R^{10}OC(O)NH-$ ;

provided that when  $R^8$  is heterocycle, attachment of  $R^8$  to V is through a substitutable ring carbon;

5

$R^9$  is independently selected from:

- a) hydrogen,
- b)  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl,  $C_1-C_6$  perfluoroalkyl, halogen,  $R^{11}O-$ ,  $R^{11}S(O)_m-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,  $R^{10}_2N-C(NR^{10})-$ , CN,  $NO_2$ ,  $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ , or  $R^{11}OC(O)NR^{10}-$ , and
- c)  $C_1-C_6$  alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br,  $R^{10}O-$ ,  $R^{11}S(O)_m-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,  $R^{10}_2N-C(NR^{10})-$ , CN,  $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ , or  $R^{11}OC(O)NR^{10}-$ ;

$R^{10}$  is independently selected from hydrogen,  $C_1-C_6$  alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

20  $R^{11}$  is independently selected from  $C_1-C_6$  alkyl and aryl;

$R^{12}$  is independently selected from hydrogen,  $C_1-C_6$  alkyl,  $C_1-C_6$  aralkyl,  $C_1-C_6$  substituted aralkyl,  $C_1-C_6$  heteroaralkyl,  $C_1-C_6$  substituted heteroaralkyl, aryl, substituted aryl, 25 heteroaryl, substituted heteraryl,  $C_1-C_6$  perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

$A^1$  and  $A^2$  are independently selected from: a bond,  $-CH=CH-$ ,  $-C\equiv C-$ ,  $-C(O)-$ ,  $-C(O)NR^{10}-$ ,  $-NR^{10}C(O)-$ , O,  $-N(R^{10})-$ ,  $-S(O)_2N(R^{10})-$ ,  $-N(R^{10})S(O)_2-$  or  $S(O)_m$ ;

- V is selected from:

- a) hydrogen,
- b) heterocycle,

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- c) aryl,
- d) C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C<sub>2</sub>-C<sub>20</sub> alkenyl,

5 provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;  
provided that when V is heterocycle, attachment of V to R<sup>8</sup> and to A<sup>1</sup> is through a substitutable ring carbon;

10 W is a heterocycle;

X is a bond, -CH=CH-, O, -C(=O)-, -C(O)NR<sup>7</sup>-, -NR<sup>7</sup>C(O)-, -C(O)O-,  
-OC(O)-, -C(O)NR<sup>7</sup>C(O)-, -NR<sup>7</sup>-, -S(O)2N(R<sup>10</sup>)-,  
-N(R<sup>10</sup>)S(O)2- or -S(=O)<sub>m</sub>-;

15 m is 0, 1 or 2;  
n is independently 0, 1, 2, 3 or 4;  
p is independently 0, 1, 2, 3 or 4;  
q is 0, 1, 2 or 3;

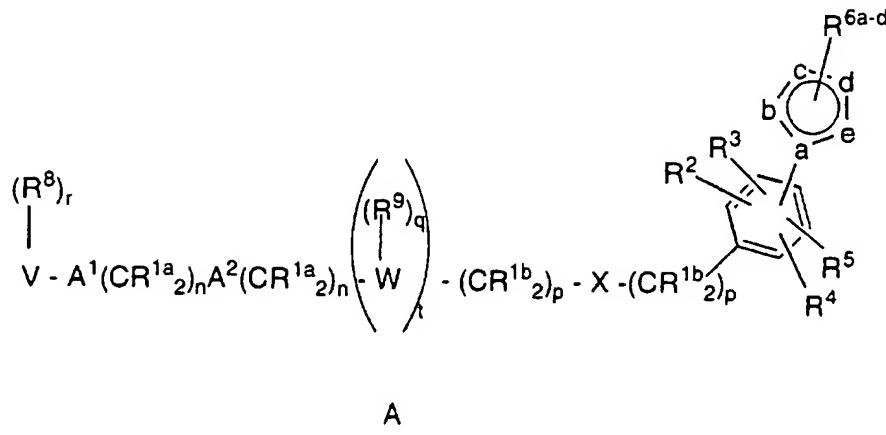
20 r is 0 to 5, provided that r is 0 when V is hydrogen; and  
t is 0 or 1;

or a pharmaceutically acceptable salt thereof.

25

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2. The compound according to Claim 1 of the formula A:



wherein:

5 a is N or C;

from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH, O or S;

10

R<sup>1a</sup> is independently selected from: hydrogen, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>1b</sup> is independently selected from:

15

- a) hydrogen,
- b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>2</sub>-C<sub>6</sub> alkenyl,
- c) unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O- and -N(R<sup>10</sup>)<sub>2</sub>;

20

R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are independently selected from:

- a) hydrogen,

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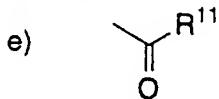
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$R^{12}O^-$ ,  $R^{11}S(O)m^-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,  
 $R^{10}O_2N-C(NR^{10})-$ , CN,  $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ , and  
 $R^{11}OC(O)-NR^{10}-$ ;

5  $R^7$  is selected from: H; C1-4 alkyl, C3-6 cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

- a) C1-4 alkoxy,
- b) aryl or heterocycle,

10 c) halogen,  
d) HO,



- f)  $-SO_2R^{11}$
- g)  $N(R^{10})_2$  or
- h) C1-4 perfluoroalkyl;

15  $R^8$  is independently selected from:

- a) hydrogen,
- b) aryl, substituted aryl, heterocycle, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 perfluoroalkyl, F, Cl, 20  $R^{10}O^-$ ,  $R^{10}C(O)NR^{10}-$ , CN,  $NO_2$ ,  $(R^{10})_2N-C(NR^{10})-$ ,  $R^{10}C(O)-$ ,  $-N(R^{10})_2$ , or  $R^{11}OC(O)-NR^{10}-$ , and
- c) C1-C6 alkyl substituted by C1-C6 perfluoroalkyl,  $R^{10}O^-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2N-C(NR^{10})-$ ,  $R^{10}C(O)-$ ,  $-N(R^{10})_2$ , or  $R^{11}OC(O)-NR^{10}-$ ;

25 provided that when  $R^8$  is heterocycle, attachment of  $R^8$  to V is through a substitutable ring carbon;

$R^9$  is independently selected from:

- a) hydrogen,
- b) C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 perfluoroalkyl, F, Cl,  $R^{11}O^-$ ,  $R^{11}S(O)m^-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,

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CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or  
R<sup>11</sup>OC(O)NR<sup>10</sup>-, and

5           c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by C<sub>1</sub>-C<sub>6</sub>  
perfluoroalkyl, F, Cl, R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-,  
(R<sup>10</sup>)<sub>2</sub>NC(O)-, CN, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-,  
-N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-;

R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

10           R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

15           R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl,  
C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl,  
heteroaryl, substituted heteroaryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl,  
2-aminoethyl and 2,2,2-trifluoroethyl;

20           A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -CH=CH-, -C≡C-,  
-C(O)-, -C(O)NR<sup>10</sup>-, O, -N(R<sup>10</sup>)-, or S(O)<sub>m</sub>;

V is selected from:

25           a) hydrogen,  
b) heterocycle selected from pyrrolidinyl, imidazolyl,  
imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl,  
quinolinyl, isoquinolinyl, triazolyl and thienyl,  
c) aryl,  
d) C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are  
30           replaced with a heteroatom selected from O, S, and N, and  
e) C<sub>2</sub>-C<sub>20</sub> alkenyl, and

provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen  
if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;

provided that when V is heterocycle, attachment of V to R<sup>8</sup> and to A<sup>1</sup> is  
through a substitutable ring carbon;

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W is a heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, triazolyl or isoquinolinyl;

5

X is a bond, O, -C(=O)-, -CH=CH-, -C(O)NR<sup>7</sup>-, -NR<sup>7</sup>C(O)-, -NR<sup>7</sup>-, -S(O)2N(R<sup>10</sup>)-, -N(R<sup>10</sup>)S(O)2- or -S(=O)m-;

m is 0, 1 or 2;

10 n is independently 0, 1, 2, 3 or 4;

q is independently 0, 1, 2 or 3;

p is 0, 1, 2, 3 or 4;

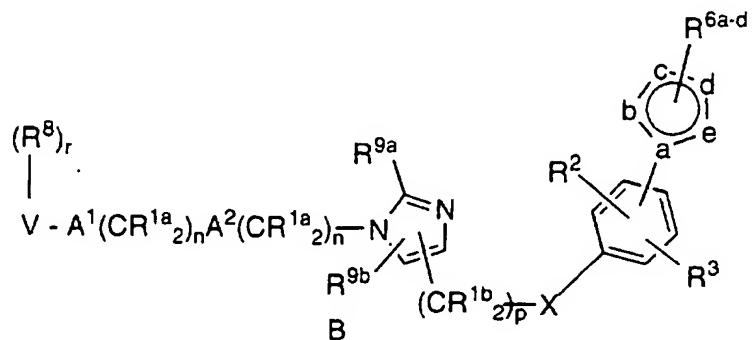
r is 0 to 5, provided that r is 0 when V is hydrogen; and

t is 0 or 1;

15

or a pharmaceutically acceptable salt thereof.

3. The compound according to Claim 1 of the formula B:



20 wherein:

a is N or C;

from 0-4 of b, c, d and e are independently N, NH, O and S, and the  
25 remaining b, c, d and e atoms are independently CH, provided that if a  
is C, then at least one of b, c, d or e is independently N, NH, O or S;

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R<sup>1a</sup> is independently selected from: hydrogen, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>1</sub>-C<sub>6</sub> alkyl;

5 R<sup>1b</sup> is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>2</sub>-C<sub>6</sub> alkenyl,
- c) unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O- and -N(R<sup>10</sup>)<sub>2</sub>;

10 R<sup>2</sup> and R<sup>3</sup> are independently selected from:

- 15 a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

20 25 30 provided that when R<sup>2</sup> or R<sup>3</sup> is unsubstituted or substituted heterocycle, attachment of R<sup>2</sup> or R<sup>3</sup> to the phenyl ring is through a substitutable heterocycle ring carbon;

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

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- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

R<sup>8</sup> is independently selected from:

- a) hydrogen,
- b) aryl, substituted aryl, heterocycle, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and
- c) C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-;

provided that when R<sup>8</sup> is heterocycle, attachment of R<sup>8</sup> to V is through a substitutable ring carbon;

R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, trifluoromethyl and halogen;

R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

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R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl,  
5 C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -CH=CH-, -C≡C-,  
10 -C(O)-, -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>C(O)-, O, -N(R<sup>10</sup>)-, or S(O)<sub>m</sub>;

V is selected from:

- a) hydrogen,
- 15 b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,
- c) aryl,
- d) C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- 20 e) C<sub>2</sub>-C<sub>20</sub> alkenyl, and

provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;  
provided that when V is heterocycle, attachment of V to R<sup>8</sup> and to A<sup>1</sup> is  
25 through a substitutable ring carbon;

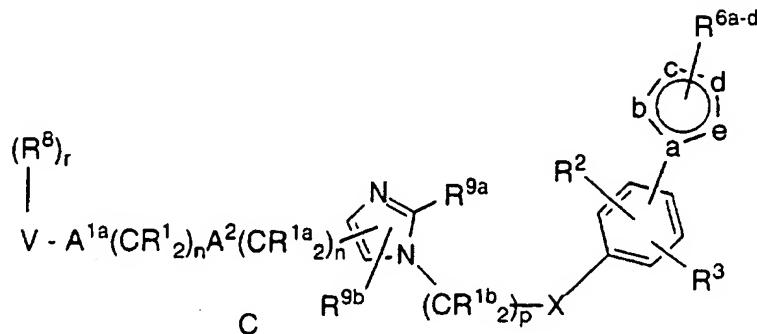
X is a bond, -CH=CH-, -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>C(O)-, -NR<sup>10</sup>-, O or -C(=O)-;

30 m is 0, 1 or 2;  
n is independently 0, 1, 2, 3 or 4;  
p is 0, 1, 2, 3 or 4; and  
r is 0 to 5, provided that r is 0 when V is hydrogen;

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or a pharmaceutically acceptable salt thereof.

4. The compound according to Claim 1 of the formula C:



5 wherein:

a is N or C;

from 0-4 of b, c, d and e are independently N, NH, O and S, and the  
10 remaining b, c, d and e atoms are independently CH, provided that if a  
is C, then at least one of b, c, d or e is independently N, NH, O or S;

R<sup>1a</sup> is independently selected from: hydrogen, C<sub>3</sub>-C<sub>10</sub> cycloalkyl,  
15 R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>1b</sup> is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>,  
F or C<sub>2</sub>-C<sub>6</sub> alkenyl,
- 20 c) unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the  
substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from  
unsubstituted or substituted aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub>  
cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O- and -N(R<sup>10</sup>)<sub>2</sub>;

25 R<sup>2</sup> and R<sup>3</sup> are independently selected from:

- a) hydrogen,

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5 b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN(R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,  
c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-,  
10 provided that when R<sup>2</sup> or R<sup>3</sup> is unsubstituted or substituted heterocycle, attachment of R<sup>2</sup> or R<sup>3</sup> to the phenyl ring is through a substitutable heterocycle ring carbon;  
15

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

20 a) hydrogen,  
 b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN(R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,  
 c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
 d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

R<sup>8</sup> is independently selected from:

- a) hydrogen,
- b) 5 aryl, substituted aryl, heterocycle, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and
- c) 10 C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,

provided that when R<sup>8</sup> is heterocycle, attachment of R<sup>8</sup> to V is through a substitutable ring carbon;

R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, trifluoromethyl 15 and halogen;

R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

20 R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, 25 C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR<sup>10</sup>-, O, -N(R<sup>10</sup>)-, or S(O)<sub>m</sub>;

30

V is selected from:

- a) hydrogen,

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b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl triazolyl and thieryl.

5      c) aryl,

5      d) C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and

5      e) C<sub>2</sub>-C<sub>20</sub> alkenyl, and

provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;

10     provided that when V is heterocycle, attachment of V to R<sup>8</sup> and to A<sup>1</sup> is through a substitutable ring carbon;

X is a bond, -CH=CH-, -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>C(O)-, -NR<sup>10</sup>-, O or -C(=O)-;

15     m is 0, 1 or 2;

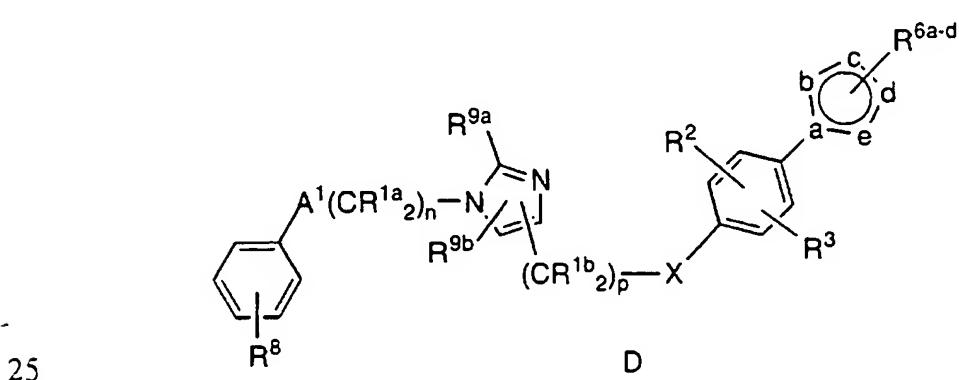
n is independently 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond, -NR<sup>10</sup>-, -NR<sup>10</sup>- or O; and

20     r is 0 to 5, provided that r is 0 when V is hydrogen;

or a pharmaceutically acceptable salt thereof.

5 The compound according to Claim 1 of the formula D:



wherein:

a is N or C;

5 from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH, O or S;

R<sup>1a</sup> is independently selected from: hydrogen, C<sub>3</sub>-C<sub>10</sub> cycloalkyl or C<sub>1</sub>-C<sub>6</sub> alkyl;

10 R<sup>1b</sup> is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>2</sub>-C<sub>6</sub> alkenyl,
- 15 c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O-, or -N(R<sup>10</sup>)<sub>2</sub>;

R<sup>2</sup> is selected from:

- 20 a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- 25 c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

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provided that when  $R^2$  is unsubstituted or substituted heterocycle, attachment of  $R^2$  to the phenyl ring is through a substitutable heterocycle ring carbon;

5  $R^3$  is selected from H, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl and CF<sub>3</sub>;

$R^{6a}$ ,  $R^{6b}$ ,  $R^{6c}$  and  $R^{6d}$  are independently selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- 10 c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-,
- 15
- 20

$R^8$  is independently selected from:

- 25 a) hydrogen,
- b) aryl, substituted aryl, heterocycle, substituted heterocycleC<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and
- c) C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- 30

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provided that when R<sup>8</sup> is heterocycle, attachment of R<sup>8</sup> to V is through a substitutable ring carbon;

R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, halogen, CF<sub>3</sub> or methyl;

5

R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

10 R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

10

R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 15 2-aminoethyl and 2,2,2-trifluoroethyl;

A<sup>1</sup> is selected from: a bond, -C(O)-, O, -N(R<sup>10</sup>)- or S(O)<sub>m</sub>;

X is a bond, -CH=CH-, -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>C(O)-, -N(R<sup>10</sup>)-, O or

20 -C(=O)-;

n is 0 or 1; provided that n is not 0 if A<sup>1</sup> is a bond, O, -N(R<sup>10</sup>)-, or S(O)<sub>m</sub>;

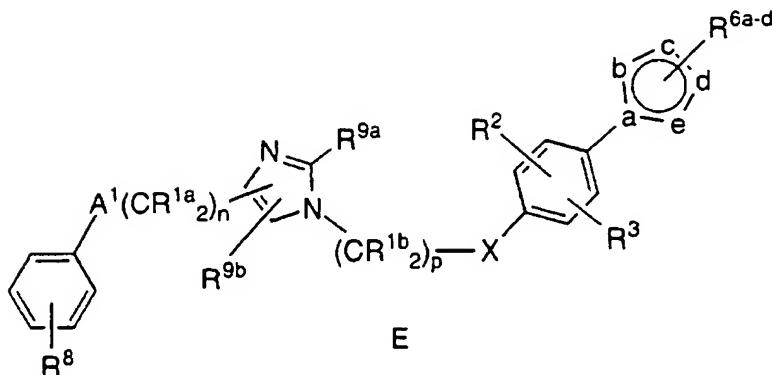
m is 0, 1 or 2; and

25 p is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

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6. The compound according to Claim 4 of the formula E:



wherein:

5 a is N or C;

from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH, O or S;

10 R<sup>1a</sup> is independently selected from: hydrogen, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F, C<sub>3</sub>-C<sub>10</sub> cycloalkyl or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>1b</sup> is independently selected from:

15 a) hydrogen,  
b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>2</sub>-C<sub>6</sub> alkenyl,  
c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O-, or  
20 -N(R<sup>10</sup>)<sub>2</sub>;

R<sup>2</sup> is selected from:

25 a) hydrogen,  
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub>

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alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,

5           c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the  
substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or  
substituted aryl, unsubstituted or substituted heterocyclic,  
10           C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,  
R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-,  
R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and  
R<sup>11</sup>OC(O)-NR<sup>10</sup>-;  
provided that when R<sup>2</sup> is unsubstituted or substituted heterocycle,  
attachment of R<sup>2</sup> to the phenyl ring is through a  
15           substitutable heterocycle ring carbon;

R<sup>3</sup> is selected from H, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl and CF<sub>3</sub>;

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

20           a) hydrogen,  
b) unsubstituted or substituted aryl, unsubstituted or  
substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub>  
alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl,  
R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-,  
25           R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>,  
or R<sup>11</sup>OC(O)NR<sup>10</sup>-,  
c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the  
substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or  
30           substituted aryl, unsubstituted or substituted heterocyclic,  
C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,  
R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-,  
R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and  
R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

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R<sup>8</sup> is independently selected from:

- a) hydrogen,
- b) 5 aryl, substituted aryl, heterocycle, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and
- c) 10 C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-;

provided that when R<sup>8</sup> is heterocycle, attachment of R<sup>8</sup> to V is through a substitutable ring carbon;

R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, halogen, CF<sub>3</sub> or methyl;

15 R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl,benzyl and aryl;

R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

20 R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 25 2-aminoethyl and 2,2,2-trifluoroethyl;

X is a bond, -CH=CH-, -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>C(O)-, -N(R<sup>10</sup>)-, O or -C(=O)-;

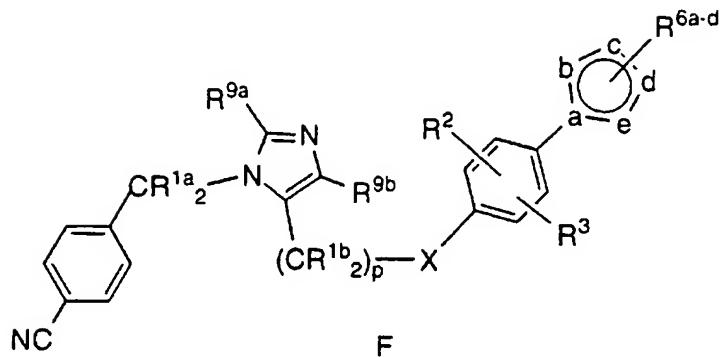
30 n is 0 or 1;

m is 0, 1 or 2; and

p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond or O;

or a pharmaceutically acceptable salt thereof.

## 7. The compound according to Claim 5 of the formula F:



wherein:

5

a is N or C;

from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a  
10 is C, then at least one of b, c, d or e is independently N, NH, O or S;

R<sup>1a</sup> is independently selected from: hydrogen, C<sub>3</sub>-C<sub>10</sub> cycloalkyl or C<sub>1</sub>-C<sub>6</sub> alkyl;

15 R<sup>1b</sup> is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub> or F,
- c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, or -N(R<sup>10</sup>)<sub>2</sub>;

R<sup>2</sup> is selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub>

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alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-;

5       c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,  
10      R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;  
provided that when R<sup>2</sup> is unsubstituted or substituted heterocycle, attachment of R<sup>2</sup> to the phenyl ring is through a  
15      substitutable heterocycle ring carbon;

R<sup>3</sup> is selected from H, halogen, CH<sub>3</sub> and CF<sub>3</sub>;

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

20      a) hydrogen,  
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,  
25      c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

30

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R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, halogen, CF<sub>3</sub> or methyl;

5 R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

10 R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

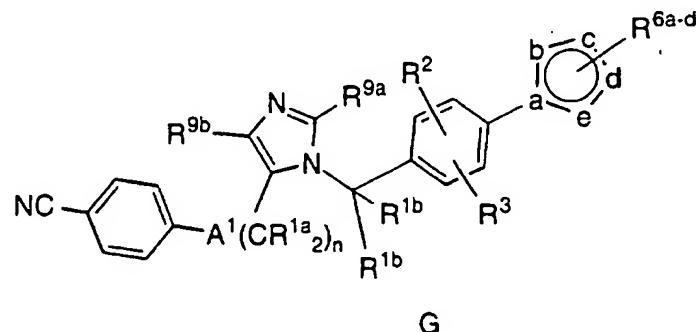
15 X is a bond, -CH=CH-, -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>C(O)-, -N(R<sup>10</sup>)-, O or -C(=O)-;

m is 0, 1 or 2; and

p is 0, 1, 2, 3 or 4;

20 or a pharmaceutically acceptable salt thereof.

8. The compound according to Claim 6 of the formula G:



25 wherein:

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a is N or C;

from 0-4 of b, c, d and e are independently N, NH, O and S, and the  
5 remaining b, c, d and e atoms are independently CH, provided that if a  
is C, then at least one of b, c, d or e is independently N, NH, O or S;

R<sup>1a</sup> is independently selected from: hydrogen, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F,  
C<sub>3</sub>-C<sub>10</sub> cycloalkyl or C<sub>1</sub>-C<sub>6</sub> alkyl;

10 R<sup>1b</sup> is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle or C<sub>3</sub>-C<sub>10</sub> cycloalkyl,
- c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl,  
heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O-, or  
15 -N(R<sup>10</sup>)<sub>2</sub>;

R<sup>2</sup> is selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or  
20 substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub>  
alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl,  
R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-,  
R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>,  
or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the  
25 substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or  
substituted aryl, unsubstituted or substituted heterocyclic,  
C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,  
30 R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-,  
R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and  
R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

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provided that when  $R^2$  is unsubstituted or substituted heterocycle,  
attachment of  $R^2$  to the phenyl ring is through a  
substitutable heterocycle ring carbon;

5     $R^3$  is selected from H, halogen,  $CH_3$  and  $CF_3$ ;

$R^{6a}$ ,  $R^{6b}$ ,  $R^{6c}$  and  $R^{6d}$  are independently selected from:

- a)    hydrogen,
- b)    unsubstituted or substituted aryl, unsubstituted or  
10    substituted heterocycle,  $C_3$ - $C_{10}$  cycloalkyl,  $C_2$ - $C_6$   
      alkenyl,  $C_2$ - $C_6$  alkynyl, halogen,  $C_1$ - $C_6$  perfluoroalkyl,  
       $R^{12}O_-$ ,  $R^{11}S(O)_m^-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,  
       $R^{10}_2N-C(NR^{10})-$ , CN,  $NO_2$ ,  $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ ,  
      or  $R^{11}OC(O)NR^{10}-$ ,
- c)    unsubstituted  $C_1$ - $C_6$  alkyl,
- d)    substituted  $C_1$ - $C_6$  alkyl wherein the substituent on the  
15    substituted  $C_1$ - $C_6$  alkyl is selected from unsubstituted or  
      substituted aryl, unsubstituted or substituted heterocyclic,  
       $C_3$ - $C_{10}$  cycloalkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  
       $R^{12}O_-$ ,  $R^{11}S(O)_m^-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,  
       $R^{10}_2N-C(NR^{10})-$ , CN,  $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ , and  
20     $R^{11}OC(O)-NR^{10}-$ ;

25     $R^{9a}$  and  $R^{9b}$  are independently hydrogen, halogen,  $CF_3$  or methyl;

$R^{10}$  is independently selected from hydrogen,  $C_1$ - $C_6$  alkyl, 2,2,2-  
trifluoroethyl, benzyl and aryl;

30     $R^{11}$  is independently selected from  $C_1$ - $C_6$  alkyl and aryl;

$R^{12}$  is independently selected from hydrogen,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$   
aralkyl,  $C_1$ - $C_6$  substituted aralkyl,  $C_1$ - $C_6$  heteroaralkyl,

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C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

5 A<sup>1</sup> is selected from: a bond, -C(O)-, O, -N(R<sup>10</sup>)-, or S(O)<sub>m</sub>;

m is 0, 1 or 2; and

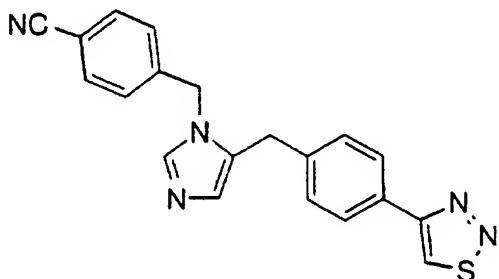
n is 0 or 1;

10 or the pharmaceutically acceptable salts thereof.

9. A compound which inhibits farnesyl-protein transferase which is:

15

1-(4-(1,2,3-Thiadiazolyl)-phenylmethyl)-5-(4-cyanobenzyl) imidazole



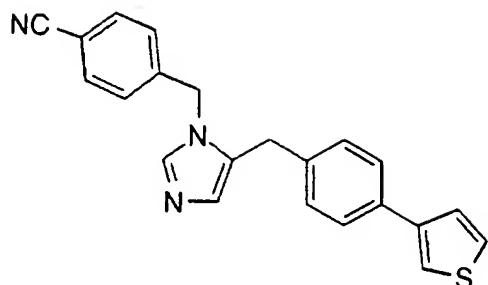
20

or a pharmaceutically acceptable salt thereof.

10. A compound which inhibits farnesyl-protein transferase which is:

25 1-(4-[Thien-3-yl]phenylmethyl)-5-(4-cyanobenzyl)imidazole

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or a pharmaceutically acceptable salt thereof.

5            11. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 1.

10          12. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 3.

15          13. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 4.

20          14. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 9.

15. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 11.

25          16. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 12.

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17. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 13.

5 18. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 14.

10 19. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 11.

15 20. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 12.

20 21. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 13.

22. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 14.

25 23. A method for treating neurofibromin benign proliferative disorder which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 11.

30 24. A method for treating blindness related to retinal vascularization which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 11.

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25. A method for treating infections from hepatitis delta and related viruses which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 11.

5 26. A method for preventing restenosis which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 11.

10 27. A method for treating polycystic kidney disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 11.

15 28. A pharmaceutical composition made by combining the compound of Claim 1 and a pharmaceutically acceptable carrier.

29. A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/05384

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 285/06, 233/02, 233/04, 233/54; A61K 31/41, 31/445

US CL :548/315.1, 127; 514/359, 397

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/315.1, 127; 514/359, 397

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Please See Extra Sheet.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3,717,655 A (GODEFROI et al.) 20 February 1973, see entire document.	1-29
A	US 3,790,594 A (MEISER et al.) 05 February 1974, see entire document.	1-29
A	US 5,352,692 A (GREIER et al.) 04 October 1994, see entire document.	1-29
A	DE 32 28 266 A1 (NATTERMANNA & CIE GMBH) 02 February 1984, see entire document.	1-29

Further documents are listed in the continuation of Box C.

See patent family annex.

• Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reasons (as specified)		
"O" document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

11 JULY 1997

Date of mailing of the international search report

28 AUG 1997

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INTERNATIONAL SEARCH REPORT

International application No.

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B. FIELDS SEARCHED

Documentation other than minimum documentation that are included in the fields searched:

Chemical Abstracts

Current Abstracts of Chemistry

Index Chemicus